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KAPPA AGONIST COMPOUNDS AND PHARMACEUTICAL FORMULATIONS THEREOF

This application is a continuation-in-part of Application Serial No. 09/478,482, filed

5 January 6, 2000, now allowed, which in turn is a divisional of Application Serial No. 09/150,369, filed September 9, 1998, now U.S. Patent No. 6,303,611, which in turn is a continuation-in-part of Application Serial No. 09/034,661 filed March 3, 1998, now U.S. Patent No. 5,945,443, which in turn is a divisional of Application Serial No. 08/899,086 filed on July 23, 1997, now U.S. Patent No. 5,744,458, which in turn is a divisional of Application Serial No. 08/796,078, filed on 10 February 5, 1997, now U.S. Patent No. 5,688,955, which in turn is a continuation-in-part of Application Serial No. 08/612,680, filed on March 8, 1996, now U.S. Patent No. 5,646,151. The disclosures of each of the foregoing applications is hereby incorporated herein by reference, in their entireties.

15

BACKGROUND OF THE INVENTION

1. Field of the Invention

This invention relates to compounds, to processes of their preparation, to pharmaceutical compositions containing them and to their medical use as agonists at kappa opioid receptors.

20

2. Reported Developments

Opium and its derivatives are potent analgesics that also have other pharmacological effects, and exert their effects by interacting with high-affinity receptors.

25 It has been shown by investigators that there are at least three major opioid receptor types in the central nervous system (hereinafter CNS) and in the periphery. These receptors, known as mu (μ), delta (δ) and kappa (κ), have distinct pharmacological profiles, anatomical distributions and functions. [See, for example: Wood, P.L., *Neuropharmacology*, 21, 487-497, 1982; Simon, E. J., *Med. Res. Rev.*, 11, 357-374, 1991; Lutz et al, *J. Recept. Res.* 12, 267-286; and Mansour et al, *Opioid I*, ed. Herz., A. (Springer, Berlin) pp. 79-106, 1993.] The δ receptors are abundant in 30 CNS and mediate analgesia, gastrointestinal motility and various hormonal functions. The μ receptors bind morphine-like drugs and mediate the opiate phenomena associated with morphine, including analgesia, opiate dependence, cardiovascular and respiratory functions, and several neuroendocrine effects.

The κ receptors have a wide distribution in CNS and mediate a spectrum of functions including the modulation of drinking, water balance, food intake, gut motility, temperature control and various endocrine functions. They also produce analgesia. [See, for example: Leander et al, J. Pharmacol. Exp. Ther. 234, 463-469, 1985; Morley et al, Peptides 4, 797-800, 5 1983; Manzanares et al, Neuroendocrinology 52, 200-205, 1990; and Iyengar et al, J. Pharmacol. Exp. Ther, 238, 429-436, 1986.]

Most clinically used opioid analgesics such as morphine and codeine act as μ receptor agonists. These opioids have well-known, undesirable and potentially dangerous dependence forming side effects. Compounds which are κ -receptor agonists act as analgesics through 10 interaction with κ opioid receptors. The advantage of these agonists over the classical μ receptor agonists, such as morphine, lies in their ability to cause analgesia while being devoid of morphine-like behavioral effects and addiction liability.

A large number of classes of compounds which act as agonists at κ opioid receptors have been described in the art including the following illustrative classes of compounds.

15 U.S. Patent No. 4,065,573 discloses 4-amino-4-phenylcyclohexane ketal compounds having analgesic activity.

U.S. Patent No. 4,212,878 discloses phenylacetamide derivatives having analgesic properties and reduced physical dependence liability properties, relative to morphine and methadone.

20 U.S. Patent No. 4,145,435 discloses N-(2-amino-cycloaliphatic)-phenylacetamide compounds having analgesic activity and narcotic antagonist activity.

U.S. Patent No. 4,098,904 discloses N-(2-amino-cycloaliphatic)-benzoamides and naphthamides useful for relieving pain.

25 U.S. Patent No. 4,359,476 discloses substituted cycloalkane-amides useful as analgesic and having low abuse liability.

U.S. Patent No. 4,438,130 discloses 1-oxa-, aza- and thia-spirocyclic compounds having analgesic activity, low physical dependence and abuse liability properties and little dysphoric inducing properties.

30 U.S. Patent No. 4,663,343 discloses substituted naphthalenyloxy-1,2-diaminocyclohexyl amides as analgesics.

U.S. Patent No. 4,906,655 discloses 1,2-cyclohexylaminoaryl amides having high kappa-opioid affinity, selectivity and potency and useful as analgesics, diuretics, anti-inflammatory and psychotherapeutic agents.

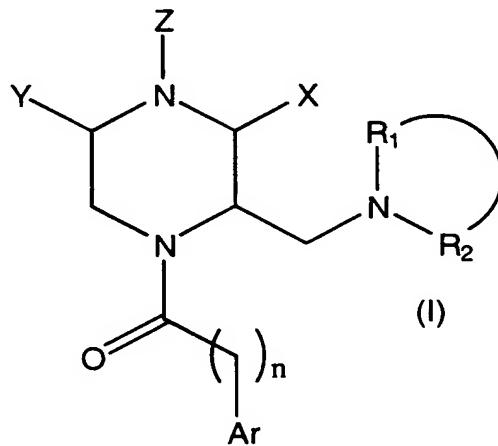
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SUMMARY OF THE INVENTION

Compounds having kappa opioid agonist activity, compositions containing them and method of using them as analgesics are provided.

In its compound aspect, the present invention provides a compound of the formulae I, II, 10 III, IIIA, IIIB, IIIB-i, IV and IVA, or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) have the following structure:



wherein

15 n is an integer from 1 to 3, with 1 being preferred;

R₁ and R₂ are together -(CH₂)_m- where m is an integer from 4 to 8,

with 4 being preferred; -CH₂CH(OH)(CH₂)₂-; -CH₂CH(F)(CH₂)₂-;

-(CH₂)₂O(CH₂)₂-; or -(CH₂)₂CH=CHCH₂-;

Ar is unsubstituted or mono- or di-substituted phenyl

20 wherein said substituents are selected from the group

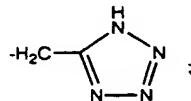
consisting of halogen, OCH₃, SO₂CH₃, CF₃, amino, alkyl,

and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl;

diphenyl methyl; or 9-fluorene;

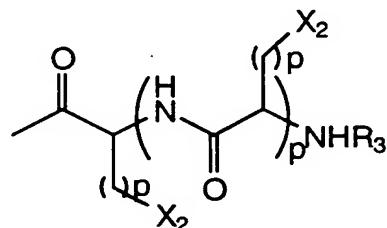
Z is -P(O)(OBn)₂; -P(O)(OH)₂; -(CH₂)_pC(O)NHOH; -(CH₂)_pCO₂H; -SO₂CH₃;

- SO_2NH_2 ;
- $\text{CO}(\text{CH}_2)_p\text{CH}(\text{NH}_2)(\text{CO}_2\text{H})$; - $\text{COCH}(\text{NH}_2)(\text{CH}_2)_p\text{CO}_2\text{H}$; - CO_2CH_3 ; - CONH_2 ;
- $(\text{CH}_2)_p\text{O}(\text{CH}_2)_p\text{CO}_2\text{H}$; - $(\text{CH}_2)_p\text{O}(\text{CH}_2)_p\text{CONHOH}$; - $(\text{CH}_2)_p\text{NHSO}_2\text{CH}_3$;
- $(\text{CH}_2)_p\text{NHC}(\text{S})\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_p\text{CO}_2\text{H}$; - $(\text{CH}_2)_p\text{SO}_3\text{H}$; or



5

or Z is



wherein

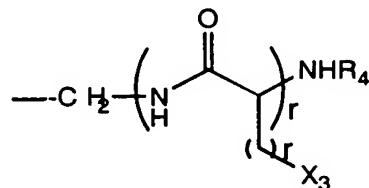
10 p is an integer from 0 to 20;

R₃ is -H or -Ac;

X₂ is -CO₂H; -NHSO₂CH₃; NHP(O)(OBn)₂; NHP(O)(OH)₂;
-OP(O)(OBn)₂; or OP(O)(OH)₂;

X and Y are independently

15 -CH₂NHSO₂CH₃, -CH₂NHP(O)(OBn)₂, -CH₂NHP(O)(OH)₂, -CH₂OP(O)(OBn)₂,
-CH₂OP(O)(OH)₂, -(CH₂)_qO(CH₂)_qCO₂H, -(CH₂)_qO(CH₂)_qSO₃H,
-(CH₂)_qO(CH₂)₂CHNHOH, -CH₂NHC(S)NHCH(CO₂H)(CH₂)_qCO₂H or



20 wherein

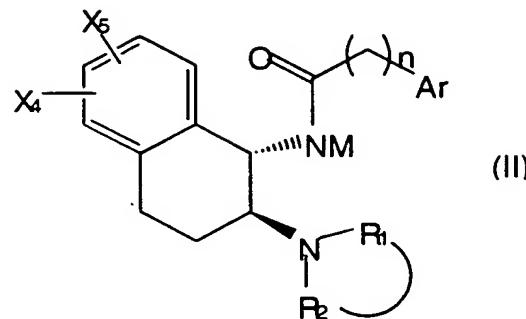
q is an integer from 1 to 20;

r is an integer from 1 to 20

R₄ is -H or -Ac

X₃ is -CO₂H; -NHSO₂CH₃; -NHP(O)(OBn)₂;
-NHP(O)(OH)₂; -OP(O)(OBn)₂; or -OP(O)(OH)₂.

The compounds of formula II have the following structure:



5

wherein

n is an integer from 1 to 3, with 1 being preferred;

R₁ and R₂ are together -(CH₂)_m-, where m is an integer from 4 to 8, with 4 being preferred; -CH₂CH(OH)(CH₂)₂-; CH₂CH(F)(CH₂)₂-;

10 -(CH₂)₂O(CH₂)₂-; or -(CH₂)₂CH=CHCH₂-;

Ar is unsubstituted or mono- or di-substituted phenyl

wherein said substituents are selected from the group

consisting of halogen, OCH₃, SO₂CH₃, CF₃, amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl;

15 diphenyl methyl; or 9-fluorene;

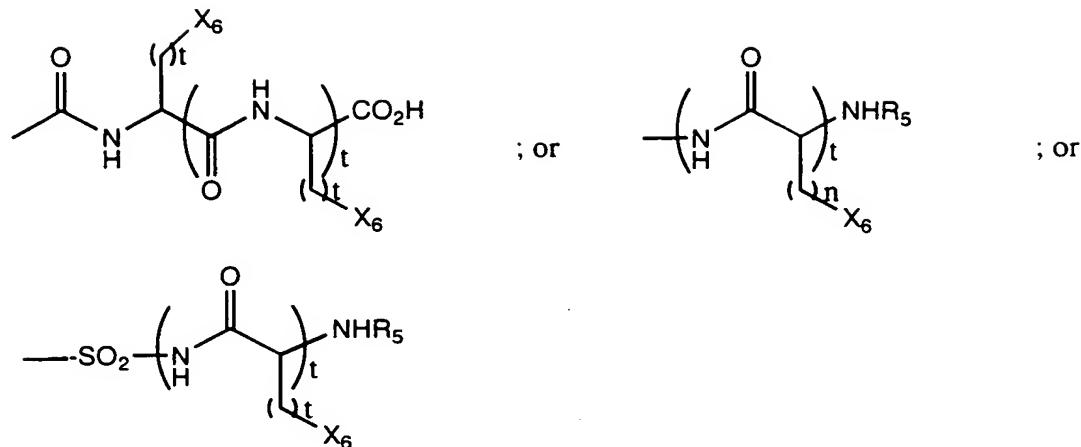
X₄ and X₅ are independently

-OP(O)(OBn)₂; -OP(O)(OH); -CO₂H; -SO₃H; -O(CH₂)_sCO₂H;

-NHSO₂CH₃; -CONH(CH₂)_sCO₂H; or -SO₂NH(CH₂)_sCO₂H;

wherein s is an integer from 1 to 5

20 or X₄ and X₅ are independently

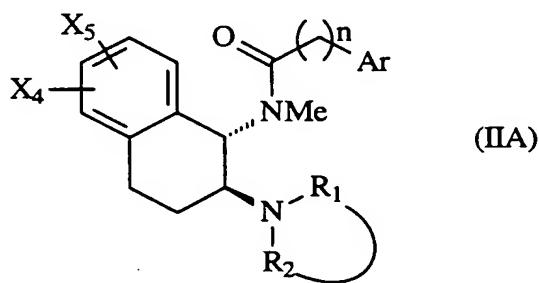


10 t is an integer from 1 to 20

5 R₅ is -H or -Ac

X₆ is -CO₂H; -NHSO₂CH₃; -NHP(O)(OBn)₂; -NHP(O)(OH)₂;
-OP(O)(OBn)₂; or -OP(O)(OH)₂.

The compounds of formula IIA have the following structure:



wherein

15 n is an integer from 1 to 3, with 1 being preferred;

R₁ and R₂ are together -(CH₂)_m-, where m is an integer from 4 to 8,

with 4 being preferred; -CH₂CH(OR)(CH₂)₂- wherein R is H, alkyl, acyl or aroyl;

CH₂CH(F)(CH₂)₂-; -(CH₂)₂O(CH₂)₂-; or -(CH₂)₂CH=CHCH₂-;

Ar is unsubstituted or mono- or di-substituted phenyl; wherein said substituents are selected from the group consisting of halogen, OCH₃, OH, SO₂CH₃, CF₃, NH₂, alkyl, CN,

20 unsubstituted and substituted sulfamoyl groups;

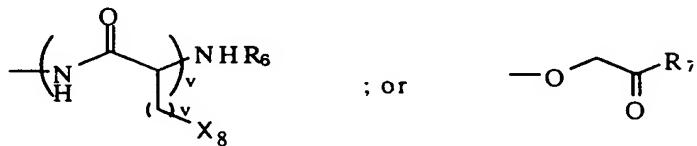
Ar may also be substituted with $-\text{NH}(\text{CH}_2)_u\text{CO}_2\text{R}'$; $-\text{NH}(\text{CH}_2)_u(\text{CH}=\text{CH})_u(\text{CH}_2)\text{CO}_2\text{R}'$; $-\text{NHCO}(\text{CH}_2)_u(\text{CH}=\text{CH})_u(\text{CH}_2)_u\text{CO}_2\text{R}'$;
 $-\text{NHP(O)(OBn)}_2$; $-\text{NHP(O)(OR)}_2$; $-(\text{CH}_2)_u\text{NHSO}_2\text{CH}_3$;
 $-(\text{CH}_2)_u\text{NHC(S)NHCH}(\text{CO}_2\text{R}')(\text{CH}_2)_u\text{CO}_2\text{R}'$; $-\text{CONHOH}$; or
5 $-(\text{CH}_2)_u\text{CONHOH}$;

wherein

u is an integer from 0 to 5;

R' is H or lower alkyl;

or Ar is



10

R_6 is -H or -Ac

X_6 is $-\text{CO}_2\text{H}$; $-\text{NHSO}_2\text{CH}_3$; $-\text{NHP(O)(OBn)}_2$; $-\text{NHP(O)(OH)}_2$;

$-\text{OP(O)(OBn)}_2$; or $-\text{OP(O)(OH)}_2$;

15 R_7 is $-\text{NH}(\text{CH}_2)_v\text{CO}_2\text{H}$; $-\text{NH}(\text{CH}_2)_v\text{CH}(\text{NH}_2)(\text{CO}_2\text{H})$; $-\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_v\text{NH}_2$;

$-\text{NH}(\text{CH}_2)_v\text{SO}_3\text{H}$; $-\text{NH}(\text{CH}_2)_v\text{PO}_3\text{H}_2$; $-\text{NH}(\text{CH}_2)_v\text{NHC(NH)NH}_2$; or

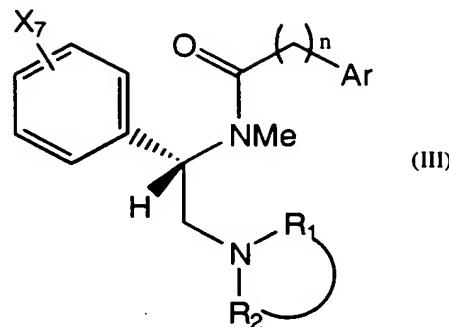
$-\text{NHCH}(\text{CO}_2\text{H})(\text{CH}_2)_v\text{CO}_2\text{H}$; and

v is an integer from 1 to 20.

20 X_4 and X_5 are independently H; halogen; OH; OCH_3 ; CF_3 ; NO_2 ; NH_2 ; amino substituted with acyl, carbamate, alkyl or aryl sulfonates; COR'' where R'' is OH, amino, alkoxy, aryloxy or heteroaryloxy.

Compounds of formula (IIA) have at least two chiral centers and may exist in more than one diastereoisomeric form. The invention includes within its scope all enantiomers, and diastereoisomers and the mixtures thereof.

25 The compounds of formula III have the following structure:



wherein

n is an integer from 1 to 3, with 1 being preferred;

R₁ and R₂ are together -(CH₂)_m-, where m is an integer from 4 to 8,

5 with 4 being preferred; -CH₂CH(OH)(CH₂)₂-;

CH₂CH(F)(CH₂)₂-; -(CH₂)₂O(CH₂)₂-; or

-(CH₂)₂CH=CHCH₂-;

Ar is unsubstituted or mono- or di-substituted phenyl

wherein said substituents are selected from the group

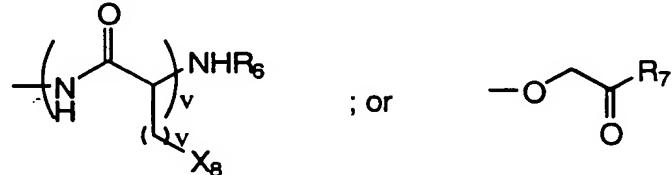
10 consisting of halogen, OCH₃, SO₂CH₃, CF₃, amino, alkyl, and 3,4-dichloro; benzothiophenyl; benzofuranyl; naphthyl; diphenyl methyl; or 9-fluorene;

X₇ is -NHSO₂CH₃; -NHP(O)(OBn)₂; -NHP(O)(OH)₂; -(CH₂)_uNHSO₂CH₃;

- (CH₂)_uNHC(S)NHCH(CO₂H)(CH₂)_uCO₂H; -CONHOH; or -(CH₂)_uCONHOH; wherein

15 u is an integer from 1 to 5

or X₇ is



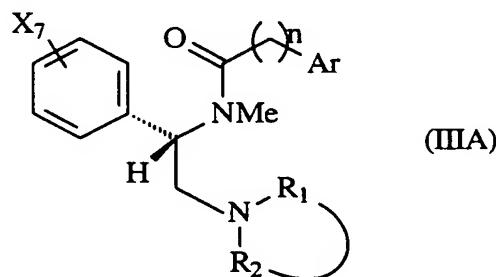
20 R₆ is -H or -Ac

X₈ is -CO₂H; -NHSO₂CH₃; -NHP(O)(OBn)₂; -NHP(O)(OH)₂;

-OP(O)(OBn)₂; or -OP(O)(OH)₂;
 R₇ is -NH(CH₂)_vCO₂H; -NH(CH₂)_vCH(NH₂)(CO₂H); -NHCH(CO₂H)(CH₂)_vNH₂;
 -NH(CH₂)_vSO₃H; -NH(CH₂)_vPO₃H₂; -NH(CH₂)_vNHC(NH)NH₂;
 -NHCH(CO₂H)(CH₂)_vCO₂H; and
 v is an integer from 1 to 20

5

The compounds of formula IIIA have the following structure:



10

wherein

n is an integer from 1 to 3, with 1 being preferred;

R₁ and R₂ are together -(CH₂)_m-, where m is an integer from 4 to 8,

with 4 being preferred; -CH₂CH(OR)(CH₂)₂-, wherein R is H, alkyl, acyl or aroyl;

15 CH₂CH(F)(CH₂)₂;-; -(CH₂)₂O(CH₂)₂;-; or -(CH₂)₂CH=CHCH₂;

Ar is unsubstituted or mono- or di-substituted phenyl; wherein said substituents are selected from the group consisting of halogen, OCH₃, OH, SO₂CH₃, CF₃, NH₂, alkyl, CN, unsubstituted and substituted sulfamoyl groups;

Ar may also be substituted with

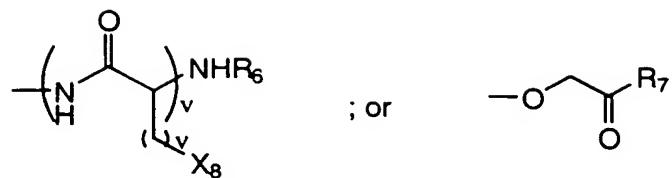
20 -NH(CH₂)_uCO₂R'; -NH(CH₂)_u(CH=CH)_u(CH₂)CO₂R';
 -NHCO(CH₂)_u(CH=CH)_u(CH₂)_uCO₂R'; -NHP(O)(OBn)₂; -NHP(O)(OR')₂;
 -(CH₂)_uNHSO₂CH₃; -(CH₂)_uNHC(S)NHCH(CO₂R')(CH₂)_uCO₂R';
 -CONHOH; or -(CH₂)_uCONHOH;

wherein

25 u is an integer from 0 to 5;

R' is H or lower alkyl;

or Ar is



15 R_6 is -H or -Ac

X_8 is $-CO_2H$; $-NHSO_2CH_3$; $-NHP(O)(OBn)_2$; $-NHP(O)(OH)_2$; $-OP(O)(OBn)_2$; or
 $-OP(O)(OH)_2$;

20 R_7 is $-NH(CH_2)_vCO_2H$; $-NH(CH_2)_vCH(NH_2)(CO_2H)$; $-NHCH(CO_2H)(CH_2)_vNH_2$;
 $-NH(CH_2)_vSO_3H$; $-NH(CH_2)_vPO_3H_2$; $-NH(CH_2)_vNHC(NH)NH_2$;
 $-NHCH(CO_2H)(CH_2)_vCO_2H$; and

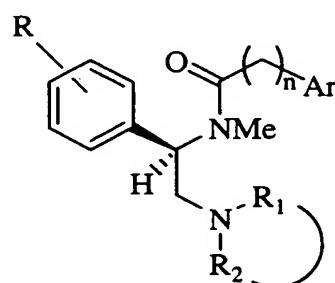
v is an integer from 1 to 20;

25 X_7 is H; halogen; OH; OCH_3 ; CF_3 ; NO_2 ; NH_2 ; amino substituted with acyl, carbamate, alkyl or aryl sulfonates; COR'' where R'' is OH, amino, alkoxy, aryloxy or heteroaryloxy.

30 Compounds of formula (IIIA) have at least one chiral center and may exist in more than one diastereoisomeric form. The invention includes within its scope all enantiomers, and diastereomers and the mixtures thereof.

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The compounds of formula IIIB have the following structure:



40

(IIIB)

45 wherein:

n is an integer from 1 to 3;

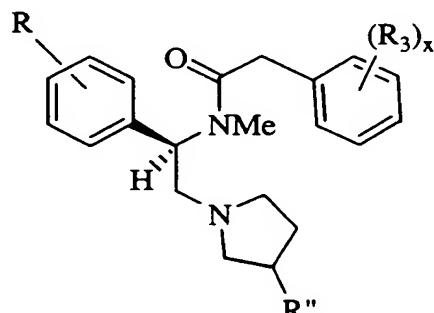
R₁ and R₂ are together alkylene of about 4 to about 8 carbons, optionally substituted with a group R', where R' is selected from -OH, halogen, -NR_aR_b, in which R_a and R_b are independently selected from hydrogen, -C(=O)R_c, -SO₂R_d and -C(=O)(CH₂)_mCO₂R_e, in which R_c and R_d are independently selected from alkyl, aryl and heteroaryl, R_e is hydrogen or alkyl and m is an integer from 1 to 3;

Ar is unsubstituted phenyl or mono-, di-, tri-, or tetra-substituted phenyl, wherein said substituents are independently selected from halogen; alkyl; alkoxy; aryloxy; aralkyloxy; alkylene dioxide; -OH; -SO₂R_f in which R_f is alkyl or aryl; -CN; haloalkyl; -NR_gR_h, in which R_g and R_h are independently selected from hydrogen, alkyl, -C(=O)R_f, -C(=O)-N(R_e)₂, -S(O)₂R_f, and -(CH₂)_y-CO₂R_e in which y is an integer from 1 to 3; -S(O)₂N(R_i)(R_j), in which R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with -CO₂R_e, aryl and aralkyl; or R_i and R_j together form -(CH₂)₂X(CH₂)₂-, where X is a direct bond, -CH₂-, -NR_e-, S or O;

R is hydrogen, halogen, -OH, alkoxy, or -NR_kR_l, where R_k and R_l are independently selected from hydrogen and alkyl.

Compounds of formula (IIIB) have at least one chiral center and may exist in more than one diastereoisomeric form. The invention includes within its scope all enantiomers, and diastereomers and the mixtures thereof.

The compounds of formula IIIB-i have the following structure.



(IIIB-i)

wherein:

x is an integer from 0 to 4;

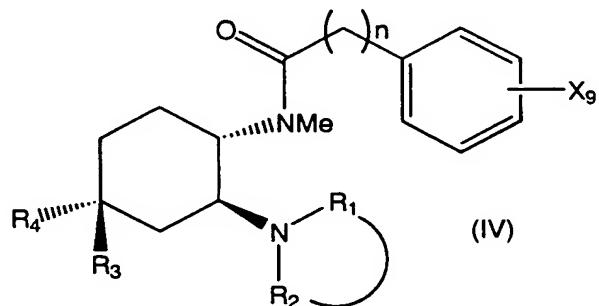
R" is hydrogen, fluoro, -OH, -NHC(=O)R_c, -NHSO₂R_d and -NHC(=O)(CH₂)_mCO₂R_e, in which R_c and R_d are independently selected from alkyl, aryl and heteroaryl, R_e is hydrogen or alkyl and m is an integer from 1 to 3

R₃ is independently selected from halogen; alkyl; alkoxy; aryloxy; aralkyloxy; alkylene dioxide; -OH; -SO₂R_f in which R_f is alkyl or aryl; -CN; haloalkyl; -NR_gR_h, in which R_g and R_h are independently selected from hydrogen, alkyl, -C(=O)R_f, -C(=O)-N(R_e)₂, -S(O)₂R_f in which R_f is alkyl or aryl, and -(CH₂)_y-CO₂R_e in which y is an integer from 1 to 3; -S(O)₂N(R_i)(R_j), in which R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with -CO₂R_e, aryl and aralkyl; or R_i and R_j together form -(CH₂)₂X(CH₂)₂-₂, where X is a direct bond, 10 -CH₂-₂, -NR_e-₂, S or O;

R is hydrogen, halogen, -OH, alkoxy, or -NR_kR_l, where R_k and R_l are independently selected from hydrogen and alkyl.

Compounds of formula (IIIB-i) have at least one chiral center and may exist in more than one diastereoisomeric form. The invention includes within its scope all enantiomers, and 15 diastereosomers and the mixtures thereof.

The compounds of formula IV have the following structure:



wherein

n is an integer from 1 to 3, with 1 being preferred;

20 R₁ and R₂ are together -(CH₂)_m-₂, where m is an integer from 4 to 8,

with 4 being preferred; -CH₂CH(OH)(CH₂)₂-₂; CH₂CH(F)(CH₂)₂-₂;

-(CH₂)₂O(CH₂)₂-₂; or -(CH₂)₂CH=CHCH₂-₂;

R₃ and R₄ are independently H; OCH₃; alkyl; or C-O(CH₂)₂;

X₉ represents 1 to 4 substituents selected from the group consisting of

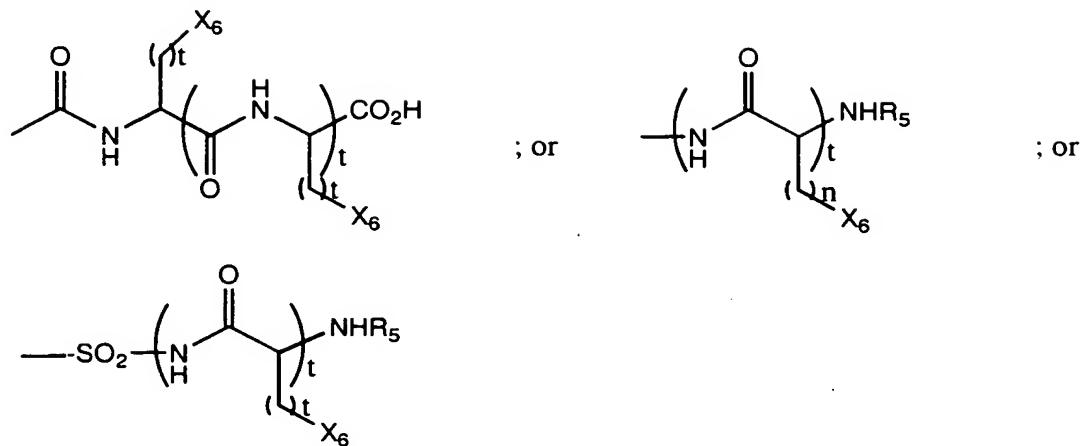
25 -halogen; -CF₃; -OCH₃; -SO₂NH(CH₂)_qCO₂H; -CONH(CH₂)_qCO₂H; -NH₂;

-NHSO₂CH₃; -NHP(O)(OBn)₂; -NHP(O)(OH)₂; -SO₂CH₃; -OP(O)(OBn)₂;

-OP(O)(OH)₂; -CO₂H; -O(CH₂)_qCO₂H; -O(CH₂)_qSO₃H; -O(CH₂)_qOPO₃H₂; wherein

q is 1 to 20;

or X_9 is



5 wherein

t is an integer from 1 to 20

R_5 is -H or -Ac

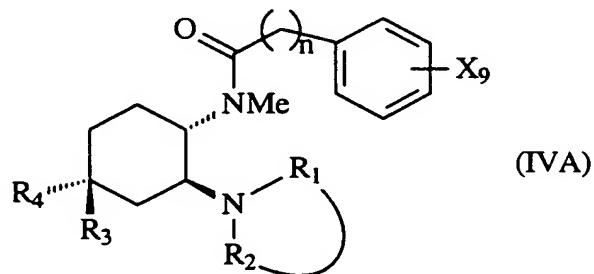
X_6 is $-\text{CO}_2\text{H}$; $-\text{NHSO}_2\text{CH}_3$; $-\text{NHP(O)(OBn)}_2$; $-\text{NHP(O)(OH)}_2$; $-\text{OP(O)(OBn)}_2$; or $-\text{OP(O)(OH)}_2$.

10

Compounds of formula (IV) have at least one chiral center and may exist in more than one diastereoisomeric form. The invention includes within its scope all enantiomers, and diastereoisomers and the mixtures thereof.

15

The compounds of formula IVA have the following structure:



wherein

20

n is an integer from 1 to 3, with 1 being preferred;

R₁ and R₂ are together -(CH₂)_m-, where m is an integer from 4 to 8, with 4 being preferred; -CH₂CH(OR)(CH₂)₂-; wherein R is H, alkyl, acyl, or aroyl; CH₂CH(F)(CH₂)₂-; -(CH₂)₂O(CH₂)₂-; or -(CH₂)₂CH=CHCH₂-; R₃ and R₄ are independently H; OCH₃; alkyl; or -O(CH₂)₂; 5 X₉ represents 1 to 4 substituents selected from the groups consisting of -halogen; -CF₃; OH, -OCH₃; -SO₂NH(CH₂)_qCH₃; -NH(CH₂)_qCOR'; -NH(CH₂)_q(CH=CH)_q(CH₂)_qCO₂R'; -NH(CH₂)_q(CH≡CH)_q(CH)_qCO₂R; -NHCO(CH₂)_q(CH=CH)_q(CH₂)_qCO₂R; and -NHCO(CH)_q(CH=CH)_q(CH)_qCO₂R'

wherein

10 q is an integer from 0 to 20
R' is OH, lower alkyl, aryl ester or aryl amide.

15 Compounds of formula (IVA) have at least one chiral center and may exist in more than one diastereoisomeric form. The invention includes within its scope all enantiomers, and diastereomers and the mixtures thereof.

The meaning of the terms used in the specification and the claims, unless otherwise denoted, are as follows.

20 The term "alkyl" as used herein alone or as part of another group, denotes optionally substituted, straight and branched chain saturated hydrocarbon groups, preferably having 1 to 12 carbons in the normal chain, most preferably lower alkyl groups. Exemplary unsubstituted alkyl groups include methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl and the like. Exemplary substituents include one or more of the following groups: halo, alkoxy, arylalkyloxy (e.g., benzyloxy), alkylthio, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkenyl, hydroxy, carboxyl (-COOH), amino, alkylamino, dialkylamino, formyl, alkylcarbonyloxy, alkylcarbonyl, heterocyclo, aryloxy, hydroxy or thiol (-SH).

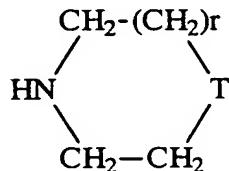
25 The term "lower alkyl" as used herein denotes such optionally substituted groups as described above for alkyl having 1 to 4 carbon atoms in the normal chain.

30 The terms "ar" or "aryl" as used herein or as part of another group, denote optionally substituted, homocyclic aromatic groups, preferably containing 1 or 2 rings and 6 to 12 ring carbons. Exemplary unsubstituted groups include phenyl, biphenyl and naphthyl. Exemplary

substituents include one or more, preferably three or fewer, nitro groups, alkyl groups as described above, and/or one or more groups described above as alkyl substituents. Preferred aryl groups are unsubstituted aryl and hydroxyaryl.

The term "aralkyl" as used herein alone or as part of another group, denotes an aryl-alkyl-
5 group wherein aryl and alkyl are as described previously. Exemplary aralkyl groups include benzyl, phenethyl and naphthylmethyl.

The terms "heterocyclo" or "heterocyclic" as used herein alone or as part of another group, denote optionally substituted fully saturated or unsaturated, aromatic or non-aromatic cyclic groups having at least one heteroatom in at least one ring, preferably monocyclic or bicyclic
10 groups having 5 or 6 atoms in each ring. Aromatic heterocyclo or heterocyclic groups are also referred to herein as "heteroaryl" groups. The heterocyclo group may, for example, have 1 or 2 oxygen atoms, 1 or 2 sulfur atoms, and/or 1 to 4 nitrogen atoms in the ring. Each heterocyclo group may be bonded through any carbon or heteroatom off the ring system. Preferred groups include those of the following formula, which may be bonded through any atom of the ring
15 system:



wherein r is 0 or 1 and T is $-\text{O}-$, $-\text{S}-$, $-\text{N}-\text{R}^8$ or $-\text{CH}-\text{R}^8$ where R^8 is hydrogen, alkyl, aryl or arylalkyl. Exemplary heterocyclo groups include the following: thienyl, furyl, pyrrolyl, pyridyl, imidazolyl, pyrrolidinyl, piperidinyl, azepinyl, indolyl, isoindolyl, quinolinyl, isoquinolinyl, benzothiazolyl, benzoxazolyl, benzimidazolyl, morpholinyl, piperazinyl, 4-alkylpiperazinyl, 4-alkylpiperidinyl, 3-alkypyrrolidinyl, oxazolyl, pyrazolyl, thiophenyl, pyridazinyl, thiazolyl, triazolyl, pyrimidinyl, 1,4-dioxanyl, benzoxadiazolyl, and benzofurazanyl. Exemplary substituents include one or more alkyl groups as described above and/or one or more groups described above as alkyl substituents.

25 The terms "halogen" or "halo" as used herein alone or as part of another group, denote chlorine, bromine, fluorine and iodine.

The term "acyl", as used herein alone or as part of another group, denotes the moiety formed by removal of the hydroxyl group from the group $-\text{COOH}$ of an organic carboxylic acid. Exemplary groups include alkylcarbonyl, arylcarbonyl, or carbocyclo- or heterocyclocarbonyl.

The term "acyloxy", as used herein alone or as part of another group denotes an acyl group as described above bonded through an oxygen linkage (-O-).

The term "alkoxy", as used herein, alone or as part of another group, denotes an alkyl-O group wherein alkyl is as described previously. Exemplary alkoxy groups include methoxy, 5 ethoxy, n-propoxy, i-propoxy, n-butoxy, pentoxy and heptoxy.

The term "aryloxy", as used herein, alone or as part of another group, denotes an aryl-O group wherein aryl is as described previously. Exemplary aryloxy groups include phenoxy and naphthoxy.

10 The term "aralkyloxy", as used herein, alone or as part of another group, denotes an aralkyl-O group wherein aralkyl is as described previously. An exemplary aralkyloxy group is benzyloxy.

15 The term "alkylene", as used herein, alone or as part of another group, denotes a straight or branched bivalent hydrocarbon chain group having from about 1 to 8 carbons. Exemplary alkylene groups include methylene (-CH₂-), ethylene (-CH₂CH₂-), propylene (-CH₂CH₂CH₂-) and butylene (-CH₂CH₂CH₂CH₂-).

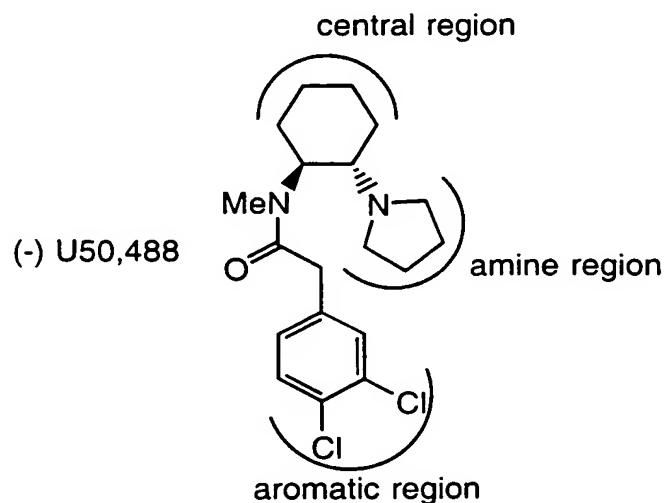
The term "alkylene dioxide", as used herein, alone or as part of another group, denotes a -O-alkylene-O- group wherein alkylene is as described previously. Exemplary alkylene dioxide groups include methylene dioxide (-O-CH₂-O-) and ethylene dioxide (-O-CH₂CH₂-O-).

20 In the formulas described herein, it is intended that when any symbol appears more than once in a particular formula or substituent, its meaning in each instance is independent of the other.

DETAILED DESCRIPTION OF THE INVENTION

25 Peripherally-acting κ agonists can be prepared by the attachment of polar groups to non-peptide κ opioid receptor selective agonists, such as the arylacetamides. In designing the peripherally-acting ligands, the introduction of the polar groups may result in either retention or enhancement of antinociceptive potency and selectivity and also may increase the polarity of the ligand sufficient to reduce or eliminate CNS penetration across the blood-brain barrier (BBB).
30 Thus, the identity and the positioning of the polar group(s) are important.

Using the prototypic arylacetamide, U50,488, as an example, the arylacetamide pharmacophore can be divided into three regions: the aromatic region, the central region, and the amine region. All three regions represent potential positions for the attachment of polar groups.

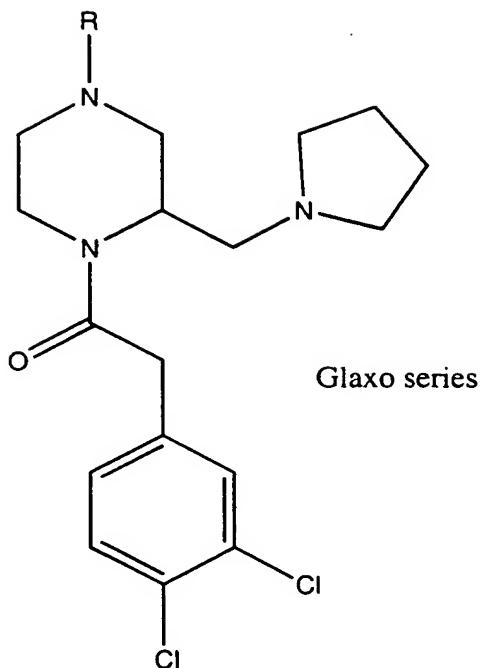


5

Compounds of formula (I) of the present invention are made as follows.

A series of novel compounds were made based on the class of arylacetamides reported by

10 Glaxo (J. Med. Chem. 1993, 36, 2075). Specifically, compound **1** can be deprotected to yield intermediate **2**, which can be derivatized by the attachment of a variety of polar groups (Scheme **1**).

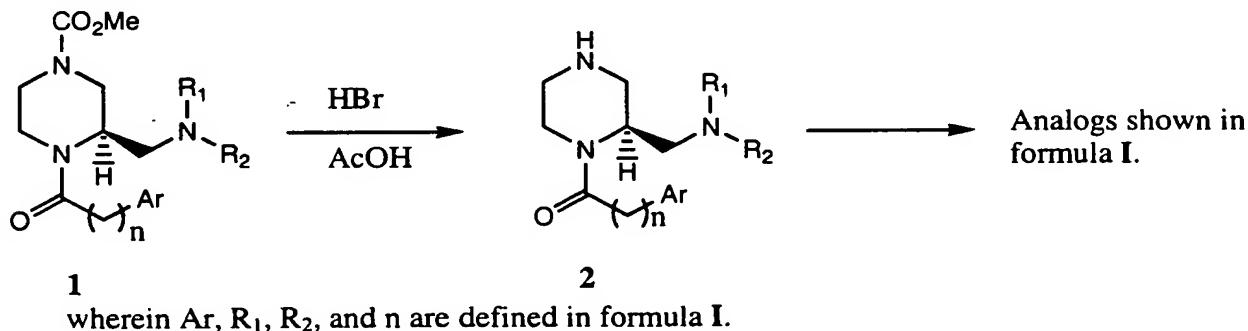


The 3'-substituted series can be prepared via **Scheme 2**. The reduction of the Schiff base intermediate formed during the cyclization to **6** is expected to be stereoselective due to the 5 directing effect of the neighboring hydroxymethyl group. Both intermediates **11** and **12** can be derivatized to confer peripheral selectivity.

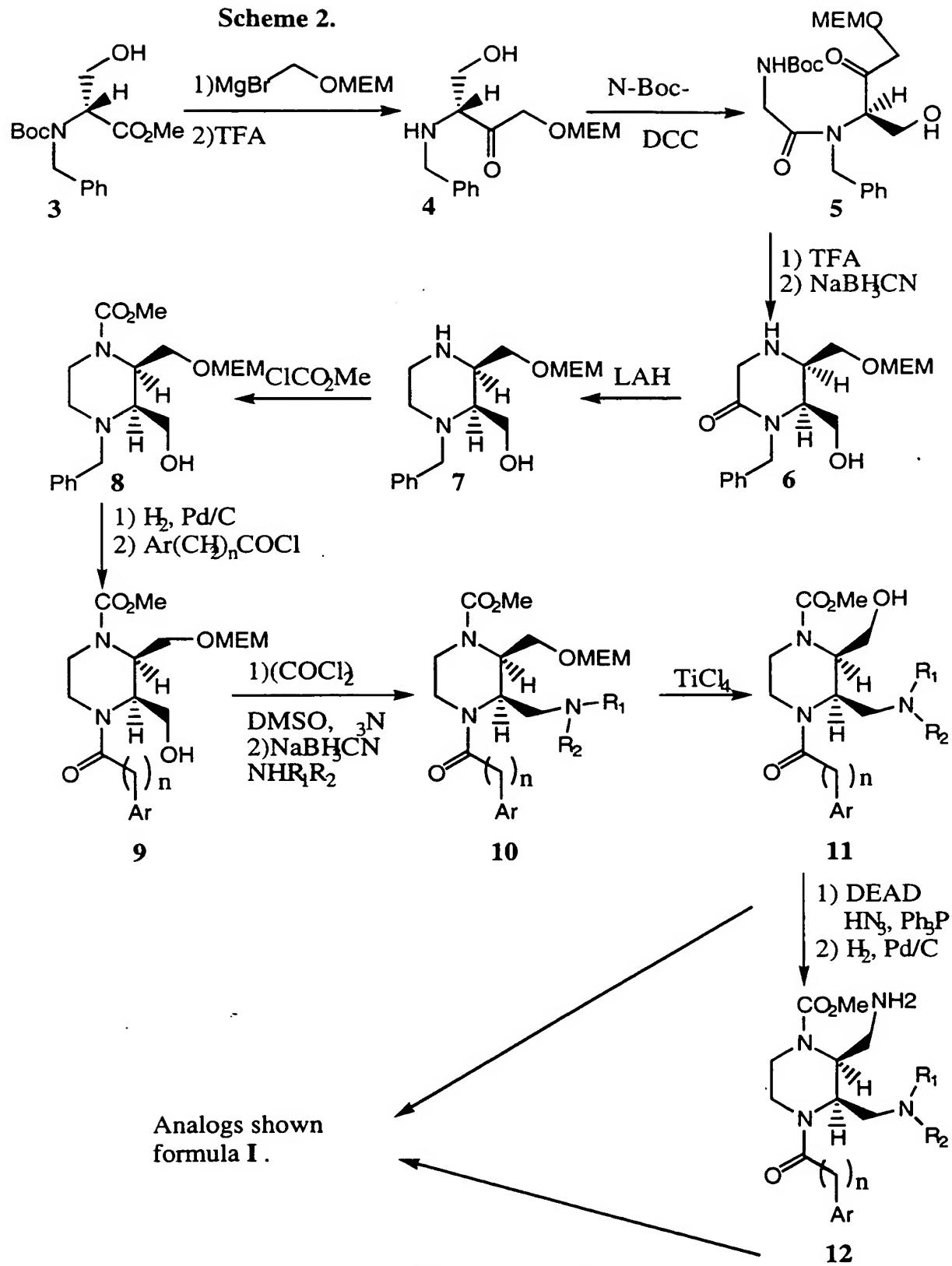
The 5'-substituted series can be prepared via **Schemes 3 and 4**. Starting from N-t-Boc-O-MEM-D-serine, the 5'-(S) series can be prepared, and starting from N-t-Boc-O-MEM-L-serine allows the preparation of the 5'-(R) series.

10

Scheme 1

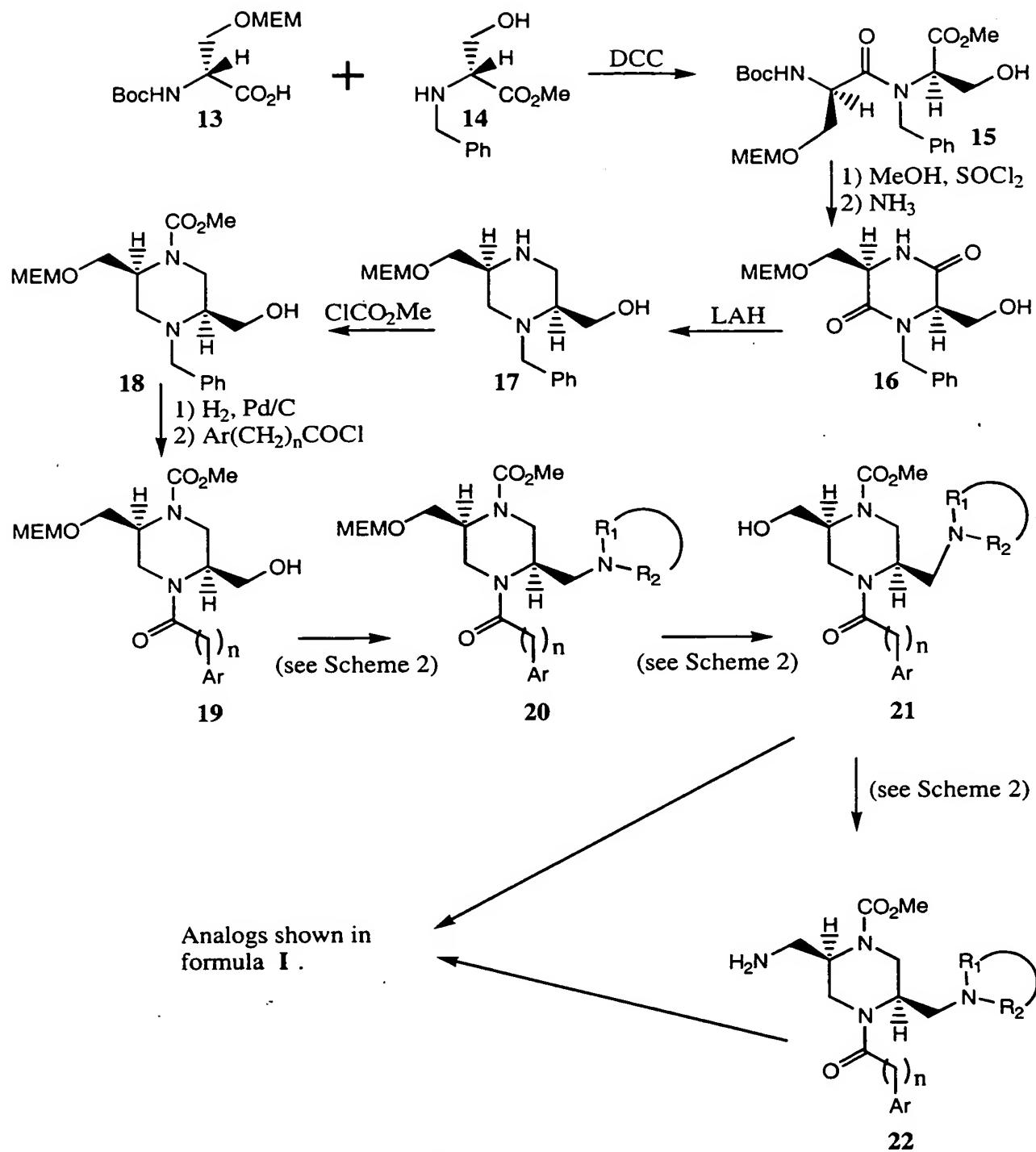


Scheme 2.



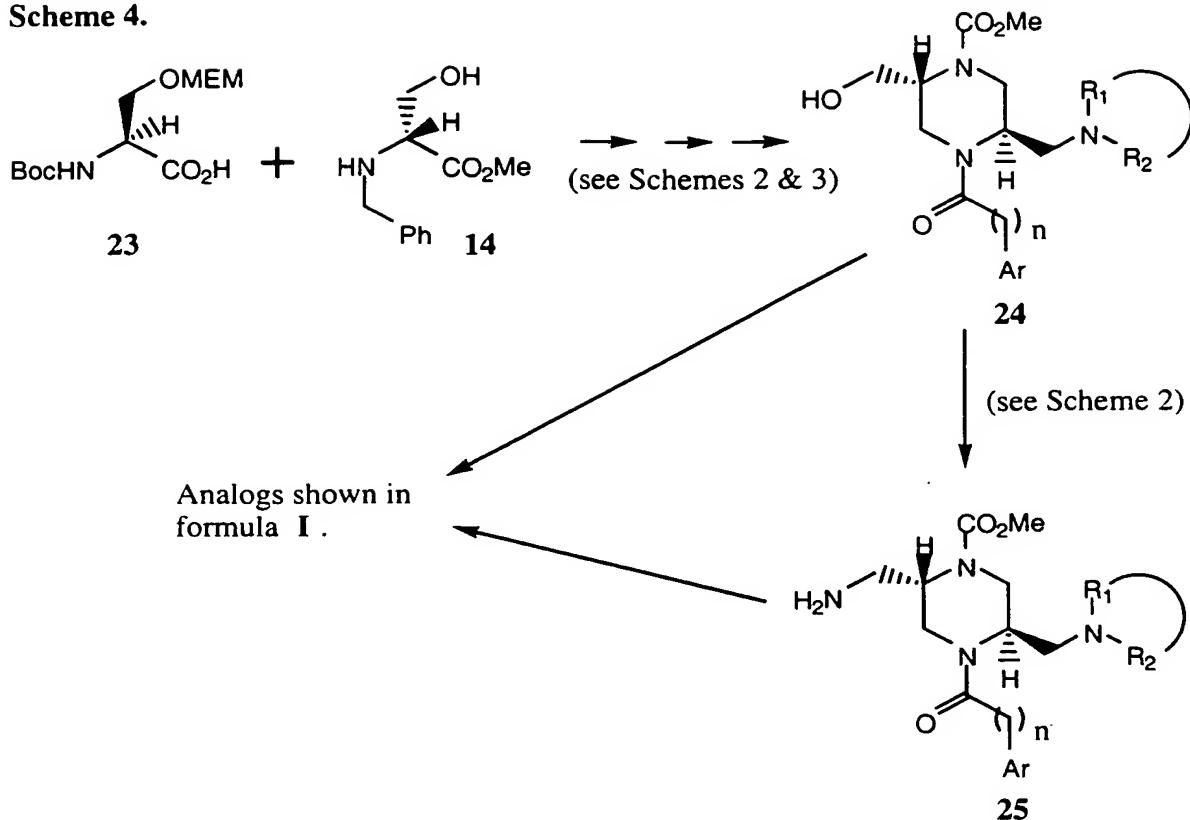
wherein Ar₁, R₁, R₂ and n are as defined in formula I.

Scheme 3.



wherein Ar₁, R₁, R₂ and n are as defined in formula I.

Scheme 4.



wherein Ar, R₁, R₂ and n are defined in formula I.

Using Schemes 1-4 the following example compounds are made.

- Intermediate 3 can be treated with t-butyl bromoacetate and deprotected to produce {4-5 [1-(3,4-Dichlorophenyl)acetyl-2R-(1-pyrrolidinyl)-methyl]piperazinyl}acetic acid (26).
- Intermediate 3 can be reacted with methane sulfonyl chloride to produce [1-(3,4-Dichlorophenyl)acetyl-4-methanesulfonyl-2R-(1-pyrrolidinyl)methyl]piperazine (27).
- Intermediate 3 can be coupled to N-t-Boc-L-aspartic acid-b-benzyl ester and deprotected to produce [4-S-Aspartic acid- α -amido-1-(3,4-dichlorophenyl)acetyl-2R-(1-pyrrolidinyl)methyl]piperazine (28).
- Intermediate 11 can be treated with t-butyl bromoacetate and deprotected to produce Methyl-[2R-(O-2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (29).

-Intermediate **11** can be coupled to to N-t-Boc-L-aspartic acid-b-benzyl ester and deprotected to produce Methyl-[2R-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**30**).

5 -Intermediate **12** can be treated with methanesulfonyl chloride to produce Methyl-[4-(3,4-dichlorophenyl)acetyl-2R-(N-methanesulfonamido)aminomethyl-3R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**31**).

-Intermediate **12** can be coupled to 2S-isothiocyanato-succinic acid-dibenzyl ester and deprotected to yield Methyl-{4-[3,4-dichlorophenyl]acetyl-3R-[1-pyrrolidinyl]methyl-2R-[N-(succinic acid-2S-thioureido)]aminomethyl}-1-piperazinecarboxylate (**32**).

10 -Intermediate **21** can be treated with t-butyl bromoacetate and deprotected to produce Methyl-[2S-(O-2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**33**).

15 -Intermediate **21** can be coupled to to N-t-Boc-L-aspartic acid-b-benzyl ester and deprotected to produce Methyl-[2S-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**34**).

-Intermediate **22** can be treated with methanesulfonyl chloride to produce Methyl-[4-(3,4-dichlorophenyl)acetyl-2S-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**35**).

20 -Intermediate **22** can be coupled to 2S-isothiocyanato-succinic acid-dibenzyl ester and deprotected to yield Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-pyrrolidinyl]methyl-2S-[N-(succinic acid-2S-thioureido)]aminomethyl}-1-piperazinecarboxylate (**36**).

-The 2R isomers of **33-34** and **35-36** can be prepared from intermediates 24 and 25, respectively to produce

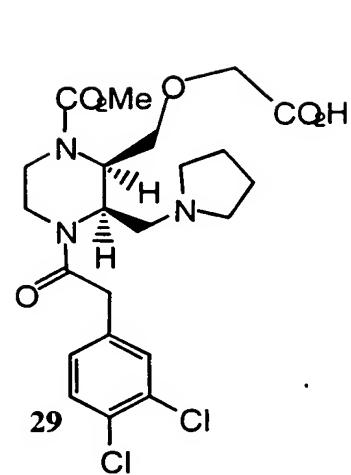
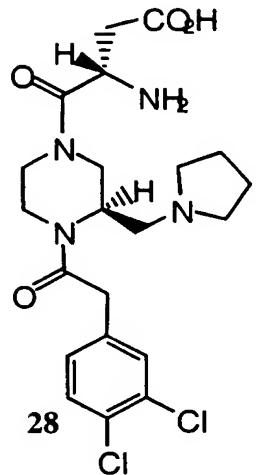
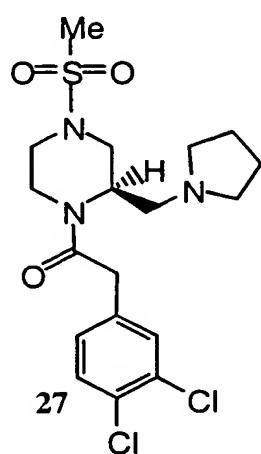
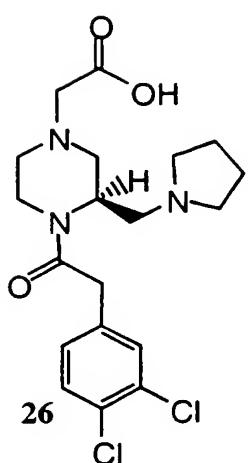
25 Methyl-[2R-(O-2-acetic acid)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**37**).

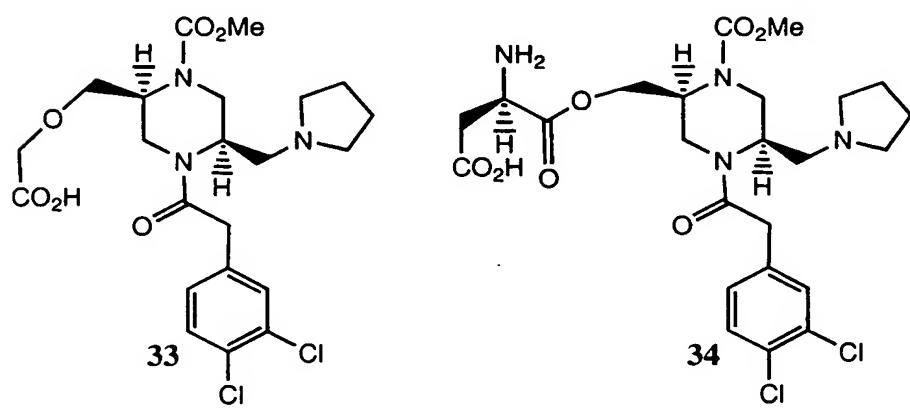
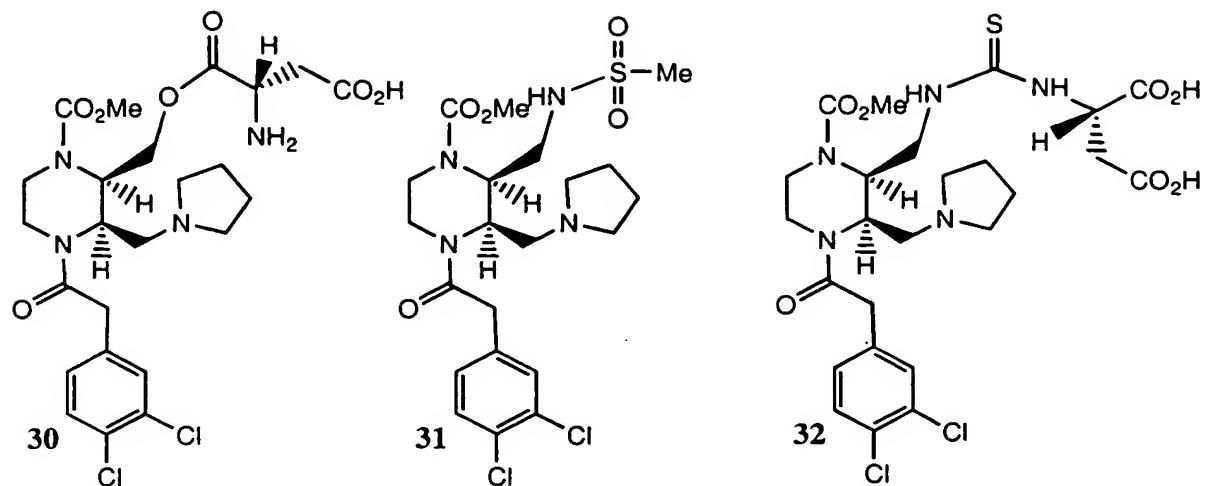
Methyl-[2R-(O-S-aspartic acid- α -acetyl)hydroxymethyl-4-(3,4-dichlorophenyl)acetyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**38**).

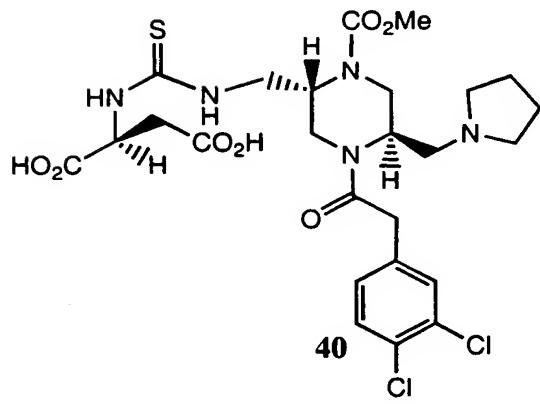
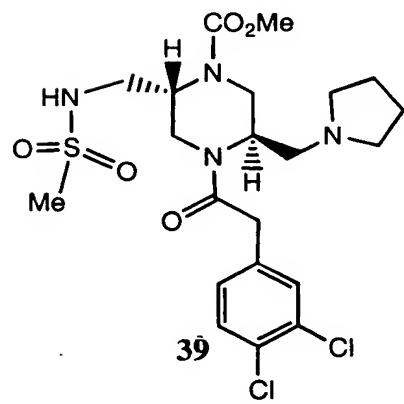
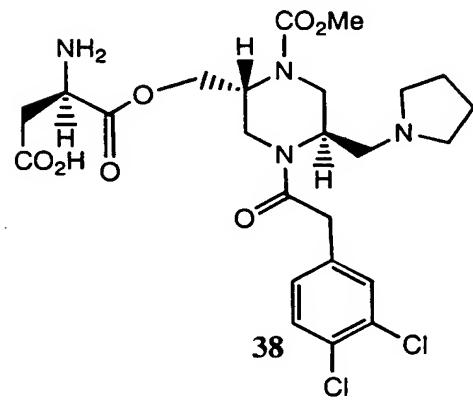
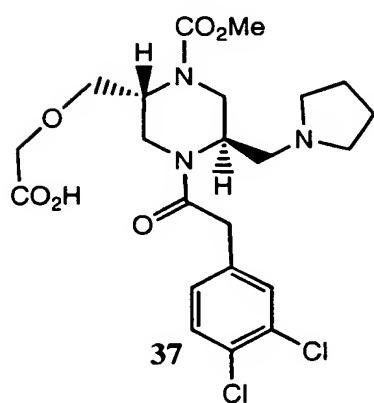
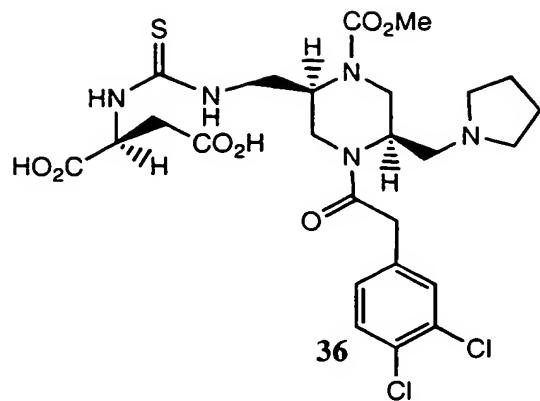
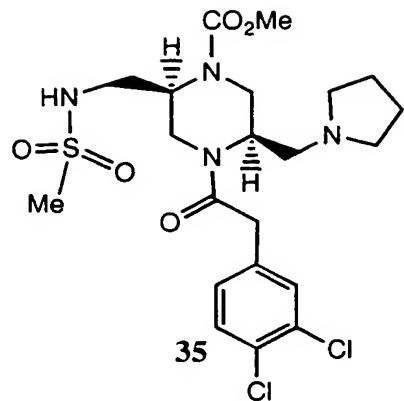
Methyl-[4-(3,4-dichlorophenyl)acetyl-2R-(N-methanesulfonamido)aminomethyl-5R-(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (**39**).

30 Methyl-{4-[3,4-dichlorophenyl]acetyl-5R-[1-pyrrolidinyl]methyl-2R-[N-(succinic acid-2S-thioureido)]aminomethyl}-1-piperazinecarboxylate (**40**).

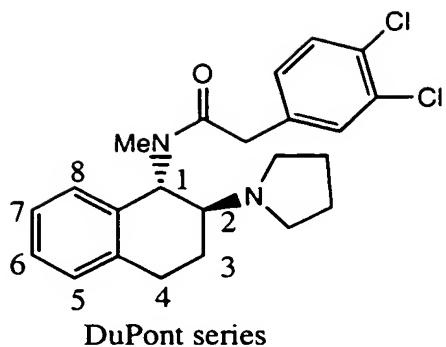
The corresponding structural formulas are shown hereunder.







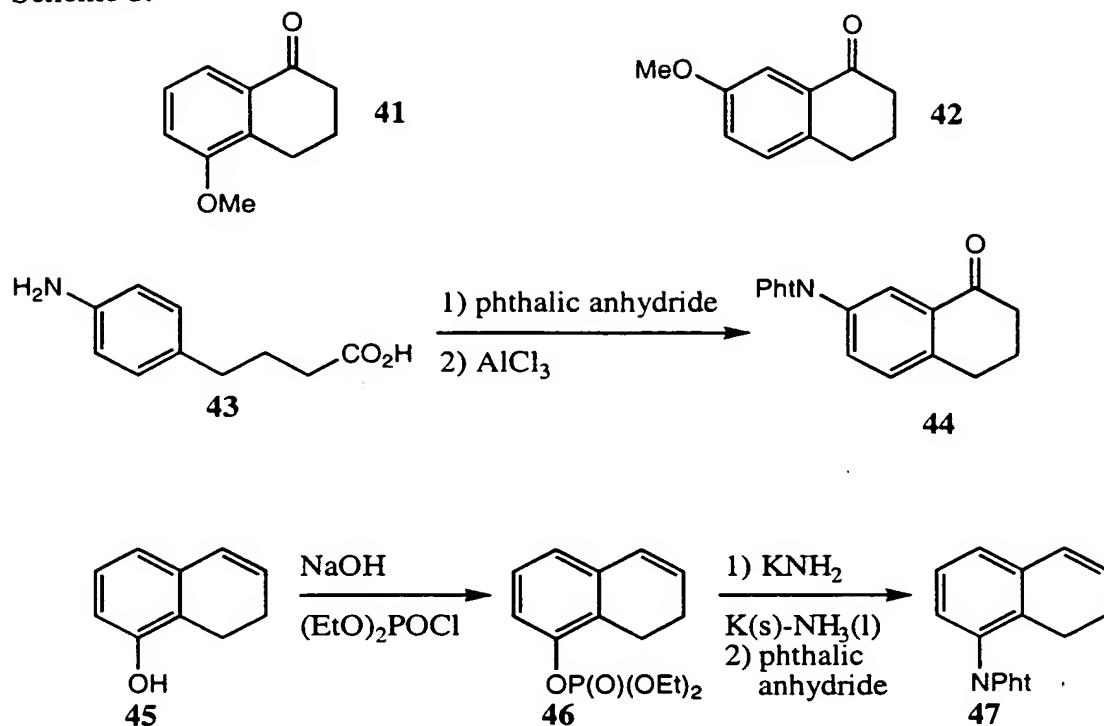
Compounds of formula II of the present invention are made by peripheralization by substitutions of the benzo portion of the tetrahydronaphthyl ring of DuPont series of compounds 5 with polar groups.



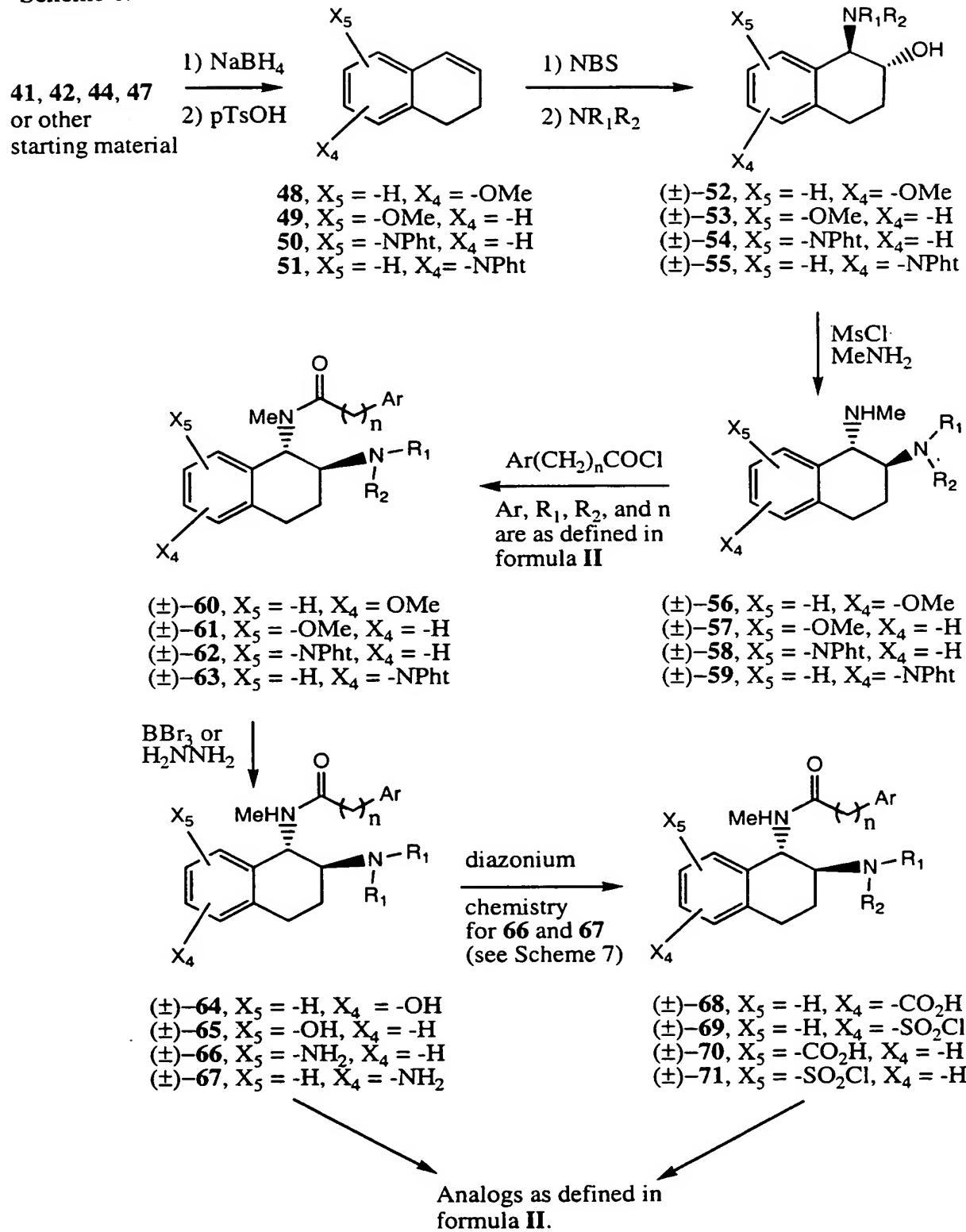
Starting material or precursors of the starting material are commercially available and thus allows regiospecific substitutions of the tetrahydronaphthyl ring (**Scheme 5**). While 5-hydroxytetralone, 6-hydroxytetralone, 7-hydroxytetralone, and 7-aminotetralone derivatives are readily available, 5-aminotetralone could be prepared from 5-hydroxytetralone (J. Org. Chem. 1972, 37, 3570).

The tetralone derivatives can be converted to dihydronaphthyl derivatives and subjected to chemistry similar to that employed in the preparation of U50,488 derivatives. The resulting compounds are racemic mixtures that can be derivatized to confer peripheral selectivity. If necessary, the final compounds or one of the intermediates can be resolved to test both enantiomers.

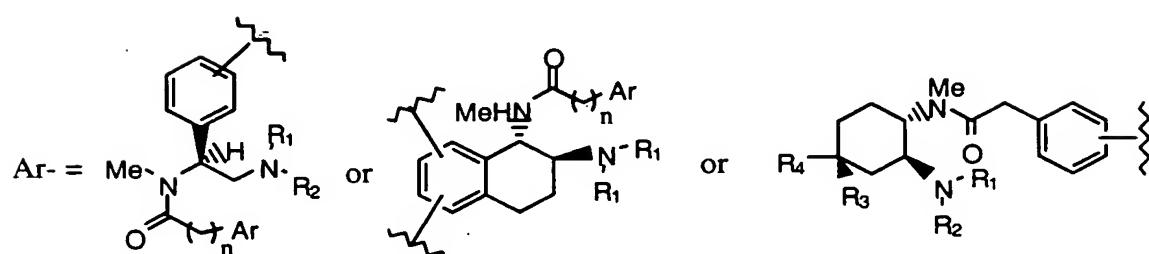
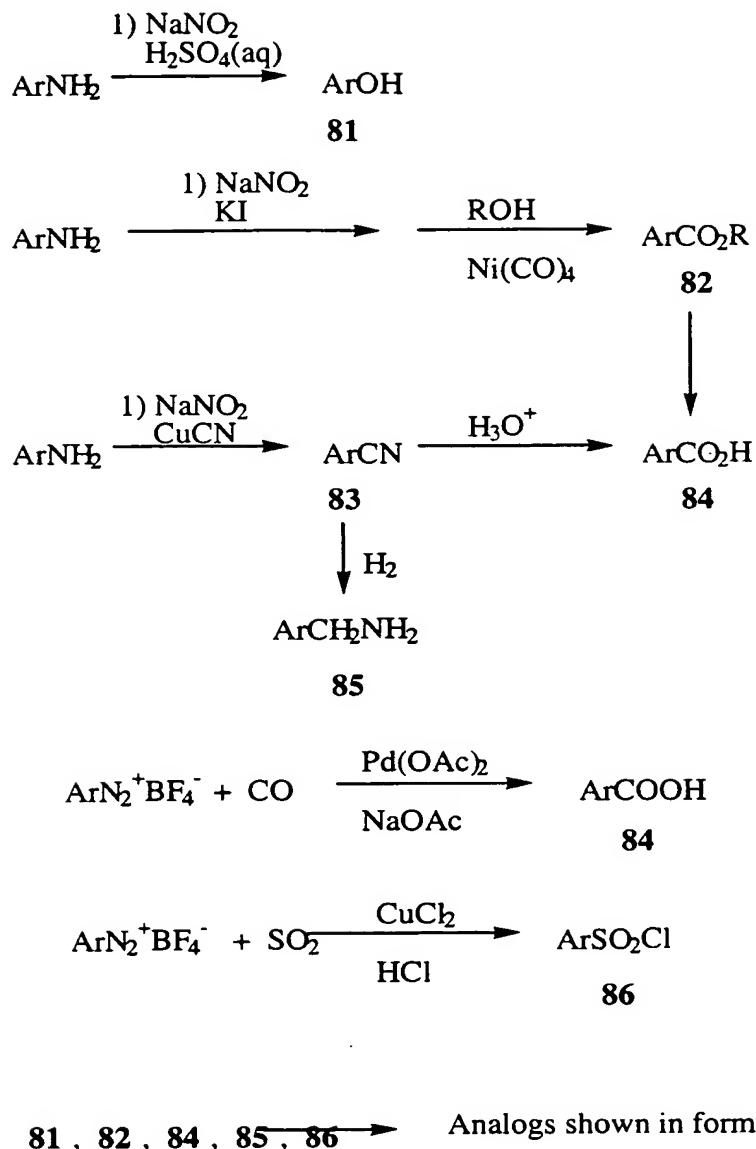
Scheme 5.



Scheme 6.



Scheme 7.



wherein R_1 , R_2 , and n are as defined in formula I.

Following the procedure shown in **Schemes 5-7**, the following example compounds are prepared.

5 -Intermediate (\pm)-**64** can be treated with t-butyl bromoacetate and deprotected to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide (**72**).

-Intermediate (\pm)-**65** can be treated with t-butyl bromoacetate and deprotected to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(O-2-acetic acid)-hydroxy-2-(1-pyrrolidinyl)naphthyl]acetamide (**73**).

10 -Intermediate (\pm)-**66** can be treated with methanesulfonyl chloride to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide (**74**).

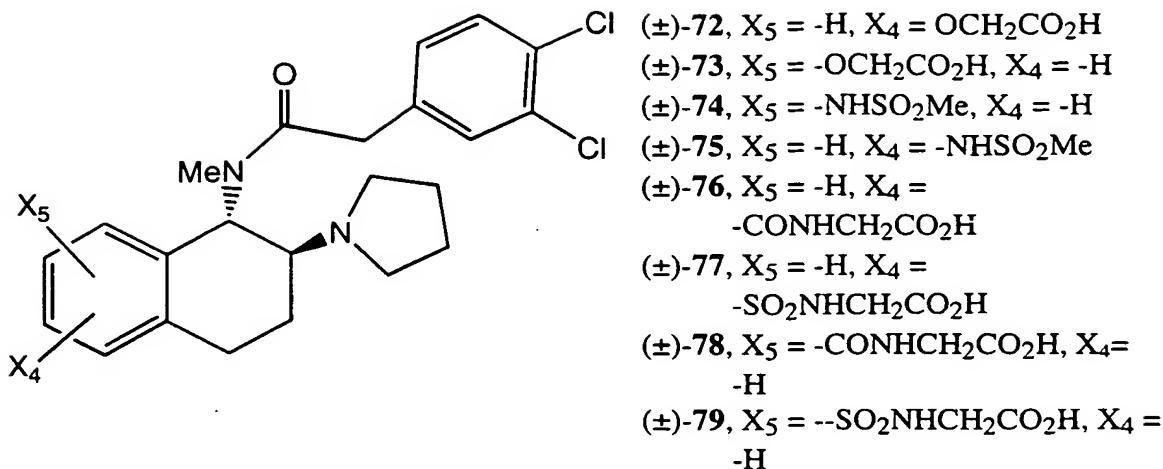
-Intermediate (\pm)-**67** can be treated with methanesulfonyl chloride to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-methanesulfonamido)-amino-2-(1-pyrrolidinyl)naphthyl]acetamide (**75**).

15 -Intermediate (\pm)-**68** can be treated with glycine benzyl ester and deprotected to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide (**76**).

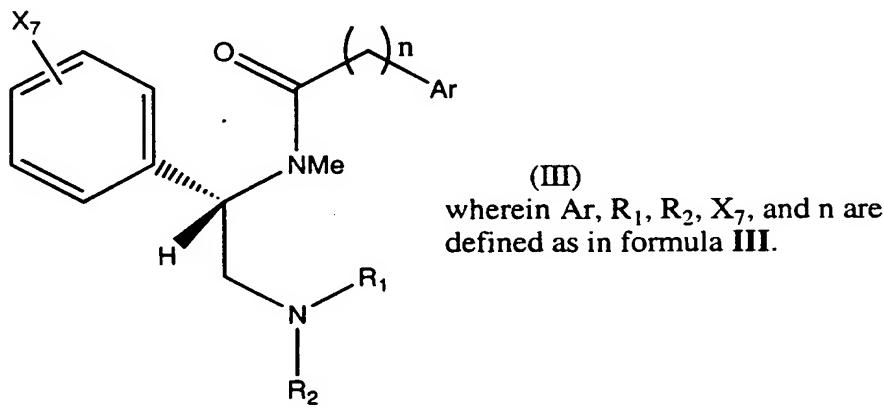
20 -Intermediate (\pm)-**69** can be treated with glycine benzyl ester and deprotected to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-5-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide (**77**).

-Intermediate (\pm)-**70** can be treated with glycine benzyl ester and deprotected to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-carboxamido-2-(1-pyrrolidinyl)naphthyl]acetamide (**78**).

25 -Intermediate (\pm)-**71** can be treated with glycine benzyl ester and deprotected to produce (\pm)-2-(3,4-dichlorophenyl)-N-methyl-N-1-[1,2,3,4-tetrahydro-7-(N-2-acetic acid)-sulfonamido-2-(1-pyrrolidinyl)naphthyl]acetamide (**79**).

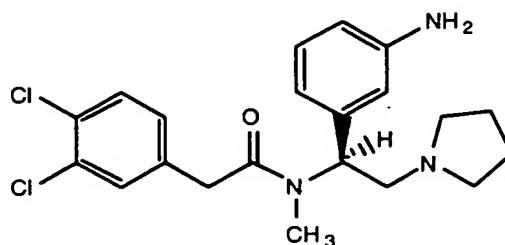


The compounds of formula III of the present invention are prepared by substituting the central phenyl ring with polar groups.



5

Compound 80 and analogues undergo a variety of diazonium-involving reactions for the attachment of polar groups (Scheme 7).



80

31

Using the procedure shown in **Scheme 7**, the following compounds are made.

-Intermediate **81** can be treated with dibenzyl phosphoryl chloride followed by

5 deprotection to produce 2-(3,4-dichlorophenyl)-N-methyl-N-{1-3-(O-phosphoryl)hydroxyphenyl-2-(1-pyrrolidinyl)ethyl}acetamide (**87**).

-Intermediate **85** can be coupled to methanesulfonyl chloride to produce

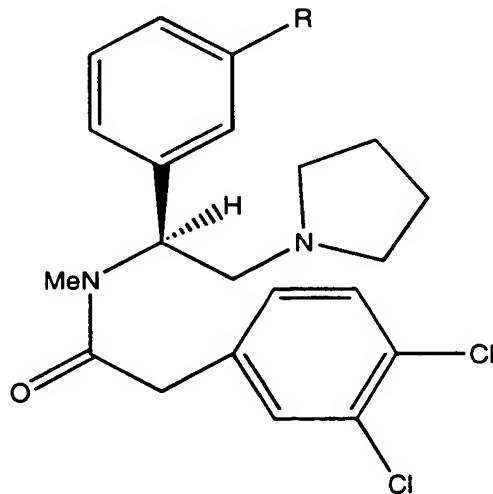
2-(3,4-dichlorophenyl)-N-methyl-N-{1-[3-(N-methanesulfonamido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl}acetamide (**88**).

10 -Intermediate **85** can be coupled to 2S-isothiocyanato succinic acid and deprotected to produce

2-(3,4-dichlorophenyl)-N-methyl-N-{1-[3-(N-succinic acid-2S-thioureido)aminomethyl]phenyl-2-(1-pyrrolidinyl)ethyl}acetamide (**89**).

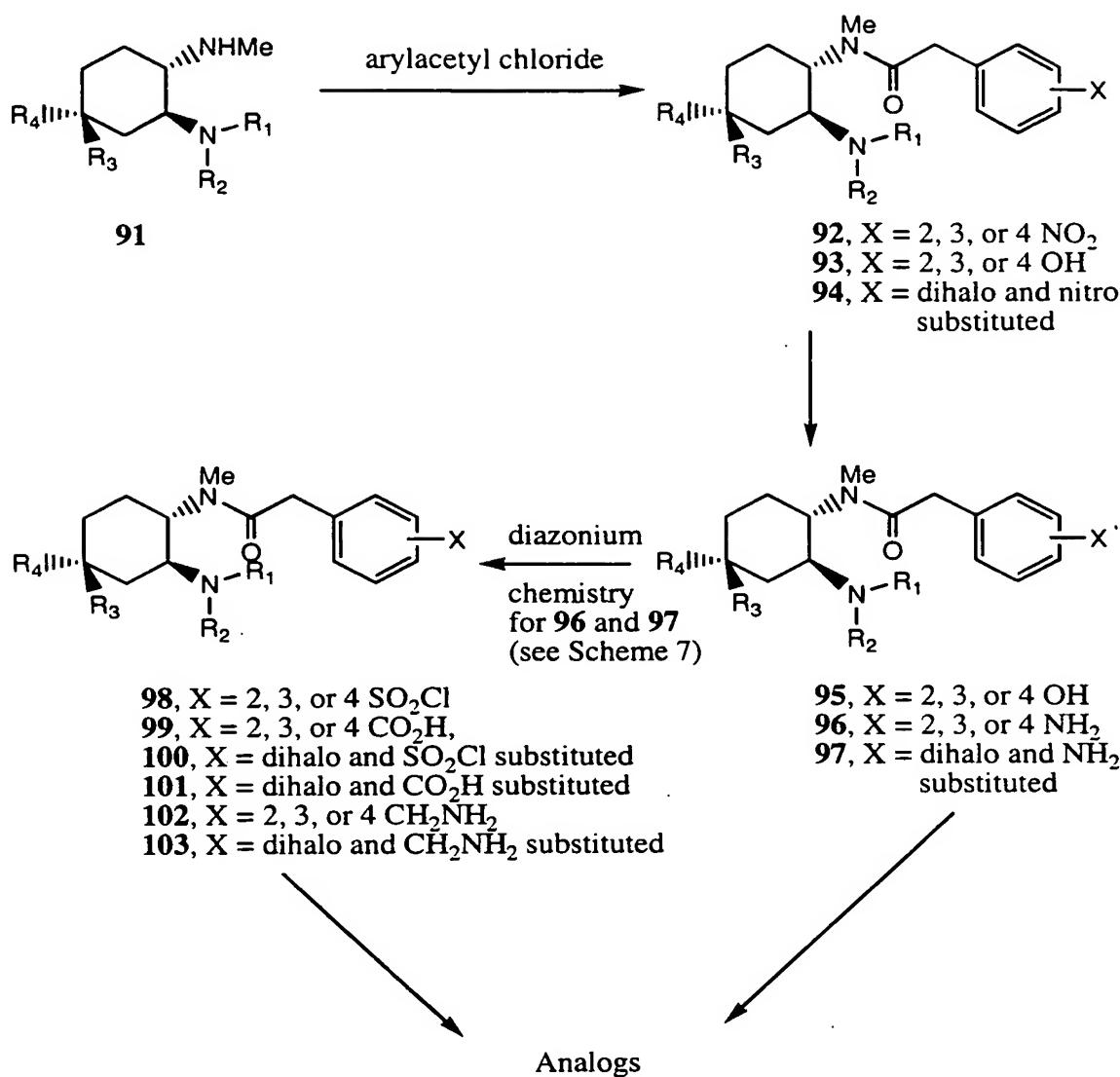
-Intermediate **80** can be treated with dibenzyl phosphoryl chloride followed by
15 deprotection to produce 2-(3,4-dichlorophenyl)-N-methyl-N-{1-3-(N-phosphoramido)aminophenyl-2-(1-pyrrolidinyl)ethyl}acetamide (**90**).

87, R = $-\text{OPO}_3\text{H}_2$
88, R = $-\text{CH}_2\text{NHSO}_2\text{Me}$
89, R = (S) $-\text{CH}_2\text{NH}(\text{C}(=\text{O})\text{S})\text{NH}(\text{C}(=\text{O})\text{CH}_2\text{CO}_2\text{H})\text{CH}_2\text{CO}_2\text{H}$
90, R = $-\text{NHPO}_3\text{H}_2$



The compounds of formula IV may be prepared by **Scheme 8**.

Scheme 8.



wherein R₁, R₂, R₃, and R₄ are defined in formulas III and IV.

The diamino intermediate 91 (J. Med. Chem. 1990, 33, 286) can be coupled to different regioisomers of nitrophenylacetic acid, which are all commercially available. Reduction of the 5 nitro group provides an amino group for the attachment of polar groups. Alternatively, the amino intermediate 95-97 readily undergo diazonium chemistry that converts the amino groups to carboxyl and sulfonyl chloride groups. This allows the polar groups to be attached via different linkers.

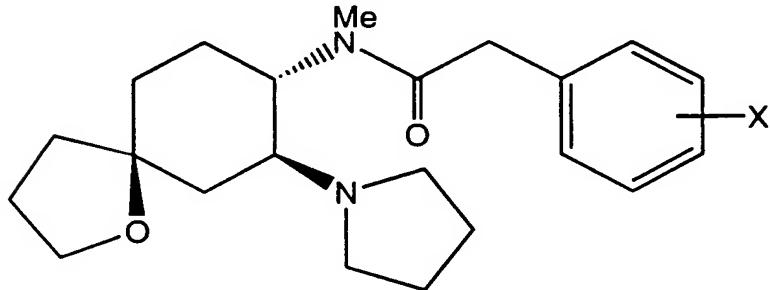
Following the procedure in **Scheme 8**, the following compounds are made.

-Intermediate **96** can be treated with methanesulfonyl chloride to produce

(-)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-methanesulfonamido)aminophenylacetamide (**104**).

5 -Intermediate **98** can be coupled to glycine benzyl ester and deprotected to yield
 (-)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)sulfonamidophenylacetamide (**105**).

-Intermediate **99** can be coupled to glycine benzyl ester and deprotected to yield
 (-)-(5 α ,7 α ,8 β)-N-methyl-N-[7-(1-pyrrolidinyl)-1-oxaspiro-[4,5]dec-8-yl]-3-(N-2-acetic acid)carboxamidophenylacetamide (**106**).



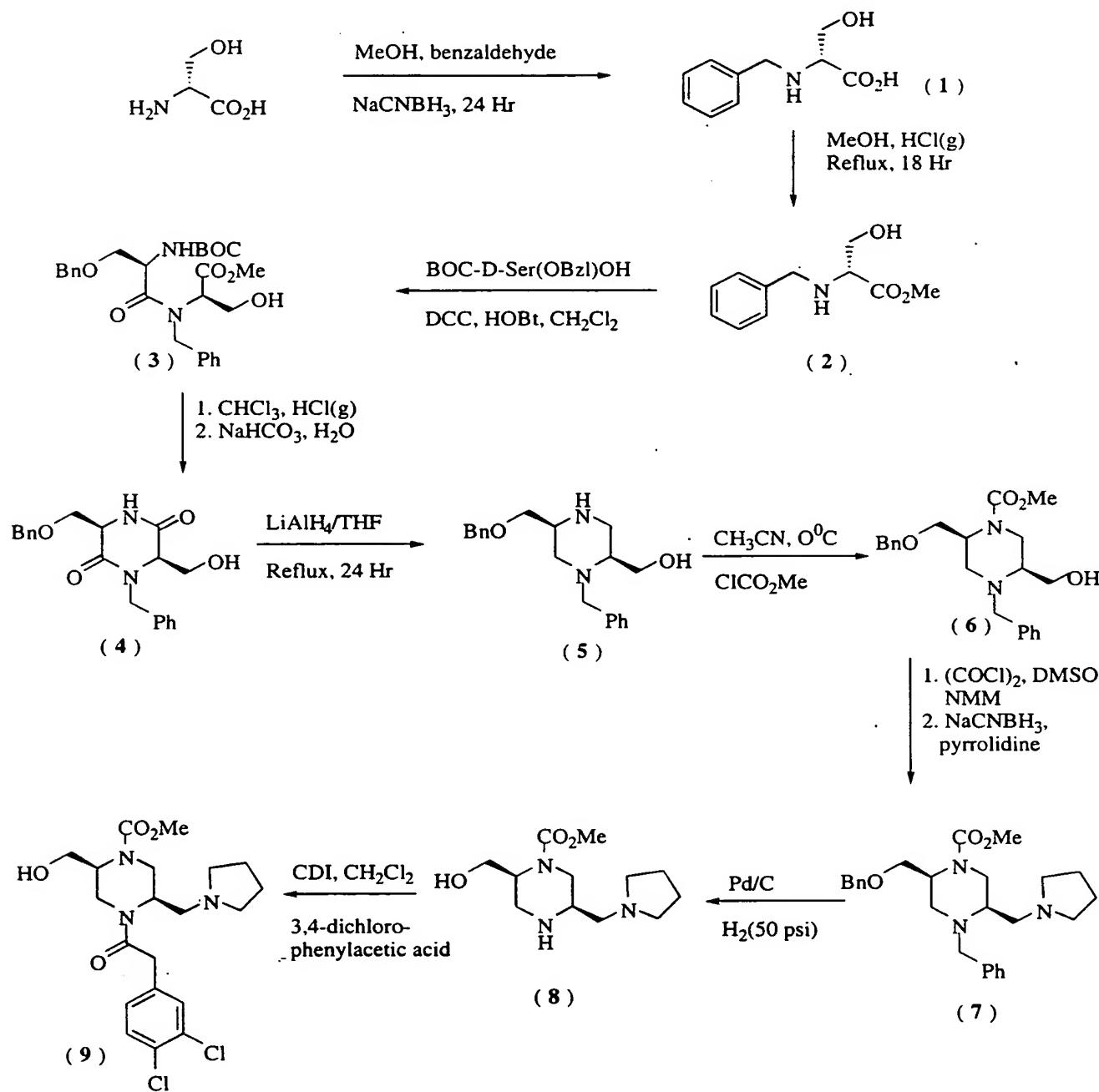
15 Compounds of the above formulas may have one or more asymmetric carbon atoms. Pure stereochemically isomeric forms of the above compounds may be obtained, and diastereoisomers isolated by physical separation methods, including, but not limited to crystallization and chromatographic methods. Cis and trans diasteriomic racemates may be further resolved into their isomers. If separated, active isomers may be identified by their activity. Such purification is not, however, necessary for preparation of the compositions or practice of the methods herein.

20 As used herein, the compounds provided herein also include pharmaceutically acceptable salts, acids and esters thereof, stereoisomers, and also metabolites or prodrugs thereof that possess activity as analgesics but do not cause substantial CNS effects when administered or applied. Metabolites include any compound that is produced upon administration of the compound and metabolism thereof.

25 More detailed preparations of the compounds of the present invention follow.

Compounds of Formula I

Preparatory for the compounds of formula I, the following intermediates were prepared.



N-Benzyl-D-serine(1)¹: To a mixture of D-serine (25.0 g, 0.237 mol) and 200 mL anhydrous methanol was added sodium cyanoborohydride (11.95 g, 0.190 mol), while maintaining the temperature at 0°C with an ice bath. Then, benzaldehyde (26.5 mL, 0.261 mol) was added to the reaction flask, dropwise, at 30°C. The mixture was stirred for 60 Hr. at room 5 temperature. Then, the mixture was filtered and rinsed with methanol (50 mL). The white solid was dried in a vacuum oven at 40°C and 10 mmHg over 2 nights: 24.5 g. The filtrate was retained and the solvent was evaporated. This oil was passed through a silica gel column (10% MeOH/CH₂Cl₂) and 3.4 g of the desired compound was isolated. The total amount of the product was 27.9g (60.0 % yield). ¹H NMR (DMSO-d₆) δ 3.25 (m, 1H, CH), 3.85 (m, 2H, CH₂), 4.11 (d, 10 2H, benzylic CH₂), 7.45-7.53 (m, 5H, ArH).

Ref.

(1) Ohfune, Y.; Kurokawa, N.; Higuichi, N.; Saito, M.; Hashimoto, M.; Tanaka, T. An efficient one-step reductive N-monoalkylation of α -amino acids. *Chemistry Letters*. 1984, 441-15 444.

N-Benzyl-D-serine methyl ester(2): Hydrogen chloride (gas) was bubbled into anhydrous methanol for 10 minutes. Then, the solution was allowed to cool to room temperature. Then, N-benzyl-D-serine (24.6 gm, 0.126 mol) was added to the reaction flask and refluxed over night 20 under dry nitrogen. Then, the solvent was evaporated and dissolved in dichloromethane (200 mL), and washed with a saturated solution of sodium bicarbonate. The dichloromethane layer was dried with magnesium sulfate and the solvent was evaporated. (23 gm, 87.2 % yield). ¹H NMR (CDCl₃) δ 3.41 (d, 1H, CH), 3.52-3.80 (dd, 2H, benzylic), 3.69 (s, 3H, OMe), 7.27 (s, 5H, ArH).

25

N-[(1,1-Dimethylethoxy)carbonyl-D-Ser-(O-Bzl)-N-benzyl-D-Ser-OMe (3): To a solution of N-boc-D-serine-(O-bzl)OH (15 g, 50.76 mmol) in anhydrous dichloromethane (200 mL) was added HOBT (7.54 g, 55.8 mmol) at 0°C under dry nitrogen. Then, DCC (11.5 g, 55.7 mmol) in dichloromethane (100 mL) was added dropwise to the reaction flask. Then, this 30 mixture was stirred for 1 Hr. Then, N-benzyl-D-serine-OMe (10 g, 47.8 mmol) in dichloromethane (100 mL) was added dropwise to the reaction flask. Then, stirred for 4 days. Then, filtered and rinsed with dichloromethane (100ml). The white precipitate was DCU and

HOBt. The filtrate was evaporated and re-dissolved in ethyl acetate (100 mL). Then, this was allowed to precipitate, overnight - more DCU. This was filtered and rinsed with ethyl acetate. Then, this was isolated on a silica gel column (20% ethyl acetate/ hexanes): an oil-17.3g, 74.3% yield. $^1\text{H NMR}$ (CDCl_3) δ 1.43 (s, 9H, t-Bu), 3.54 (t, 1H, OH), 3.72 (s, 3H, OMe), 3.75 (dd, 2H, 5 CH₂) 3.79 (dd, 2H, CH₂), 4.41 (d, 2H, CH₂ benzylic), 4.43 (d, 2H, CH₂ benzylic), 7.27-7.30(m, 10H, ArH).

(2R,5R)-2-((BenzylOxy)methyl)-5-(Hydroxymethyl)-4-(phenylmethyl)-3,6-piperazine dione(4)²:

10 Into anhydrous chloroform (300 mL) was bubbled hydrogen chloride (gas). Then, the dipeptide (3) (13.5 g, 27.7 mmol) in chloroform (100 ml) was added to the reaction flask. The flask was stoppered and stirred for 64 Hr. Then, a saturated solution (100 ml) of sodium bicarbonate was added and stirred vigorously for 48 Hr. The cyclization was completed at this point. The organic layer was separated from the aqueous layer in a 1L separatory funnel. The 15 product was isolated from a silica gel column, eluting with dichloromethane-methanol-0.88 ammonia (96:2:2) to give (4) as an amorphous solid (6.0 g, 61.1% yield). $^1\text{H NMR}$ (CDCl_3) δ 3.72-3.96 (m, 7H), 3.97-5.24 (dd, 2H, CH₂ benzylic), 4.45 (dd, 2H, CH₂ benzylic), 7.15-7.30 (m, 10H, ArH); MS (FAB) m/e 355 (MH^+).

20 Ref.

(2) Williams, T. M.; Ciccarone, T. M.; MacTough, S. C. and et al. 2-Substituted piperazines as constrained amino acids. *J. Med. Chem.* **1996**, 39, 1345-1348.

25 (2S,5S)-2-((BenzylOxy)methyl)-4-(phenylmethyl)-5-piperazinemethanol(5): A suspension of lithium aluminum hydride (0.9 g, 23.7 mmol) in anhydrous tetrahydrofuran (40 mL) was treated with a solution of piperazinedione 4 (2.1 g, 5.92 mmol) in anhydrous tetrahydrofuran (200 mL). The reaction mixture was heated at reflux for 24 Hr and then, stirred at room temperature for 12 Hr. Water (10 mL) was added followed by aqueous sodium hydroxide (1N, 10 mL) and water (10 mL). The mixture was filtered, and the filtrate was evaporated to 30 give 5 (1.67 g, 86.4% yield) as a viscous oil. $^1\text{H NMR}$ (CDCl_3) δ 2.58 (dd, 2H, CH₂), 2.61 (t, 1H, OH), 3.10 (dd, 2H, CH₂), 3.25 (dd, 2H, CH₂), 3.50 (dd, 2H, CH₂), 3.74 (s, 2H, CH₂), 4.41 (dd, 2H, CH₂ benzylic), 7.20-7.30 (m, 10H, ArH).

(2S,5S)-Methyl 2-[(BenzylOxy)methyl]-5-(hydroxymethyl)-4-(phenylmethyl)-1-piperazine carboxylate (**6**)³: A solution of **5** (1.67 g, 5.11 mmol.) in acetonitrile (20 mL) was treated with a solution of methyl chloroformate (0.532 g, 5.63 mmol) in acetonitrile (10 mL) at 0°C. The mixture was stirred at ambient temperature for 30 min., and then aqueous sodium carbonate solution (15 mL) was added. The organic solvent was removed, and the aqueous residue was extracted with chloroform (3x10 mL). The combined organic extracts were washed with aqueous sodium carbonate solution (10 mL), dried, and evaporated to give **6** (1.52 g, 77.3% yield) as an oil. ¹H NMR (CDCl₃) δ 2.54 (dd, 2H, CH₂), 2.45 (t, 1H, OH), 2.72 (dd, 2H, CH₂), 3.51 (dd, 2H, CH₂), 3.67 (dd, 2H, CH₂), 3.69 (s, 3H, OMe), 3.81 (dd, 2H, CH₂), 4.44 (dd, 2H, CH₂ benzylic), 7.17-7.31 (10H, ArH).

(2S,5S)-Methyl 2-[(BenzylOxy)methyl]-5-[(1-pyrrolidinyl)methyl]-4-(phenylmethyl)-1-piperazinecarboxylate(**7**)³: A solution of oxalyl chloride (0.545 mL, 6.24 mmol) in dichloromethane (10 mL) at -65°C was treated with a solution of dimethyl sulfoxide (1.14 mL, 16.0 mmol) in dichloromethane (5 ml) maintaining the reaction temperature below -65°C. The mixture was stirred at -70 °C for 10 min, and then a solution of the piperazinemethanol (**6**: 2 g, 5.19 mmol) in dichloromethane (20 mL) was added at such a rate that the reaction temperature was maintained below -65°C. The reaction mixture was stirred at -65°C for 3 Hr, and a solution of N-methylmorpholine (1.42 mL, 12.91 mmol) in dichloromethane (5 mL) was added. The mixture was stirred at -20 °C for 45 min and then washed with ice-cold hydrochloric acid (0.01 N, 100mL and 50mL), dried, evaporated, and placed on a high vacuum pump overnight. The residue was dissolved in methanol (10 mL) and was added to a solution of pyrrolidine (0.91 mL, 10.94 mmol) in methanol (10 mL) at -10 °C, which had been adjusted to pH 6.0 by the addition of methanolic hydrogen chloride. Sodium cyanoborohydride (0.67 g, 10.66 mmol) and 4-Å molecular sieves (0.66 g) were added, and the mixture was stirred at ambient temperature for 18 Hr. The mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in aqueous sodium carbonate (1M, 25mL) and extracted with dichloromethane (2x50 mL). The product was isolated from a silica gel column, eluting with dichloromethane-methanol (98:2) to give (**7**: 1.0 g, 23.0 % yield). ¹H NMR (CDCl₃) δ 1.75 (m, 4H, CH₂CH₂), 2.46 (m, 3H), 2.48 (m, 4H, CH₂CH₂), 2.55 (dd, 2H, CH₂), 2.70-2.85 (m, 3H), 3.41 (dd, 2H, CH₂), 3.69 (s, 3H,

OMe), 4.10 (m, 1H), 4.20 (m, 1H), 4.41 (dd, 2H, CH₂ benzylic), 7.10-7.31 (m, 10H, ArH); MS (FAB) m/e 438 (MH⁺).

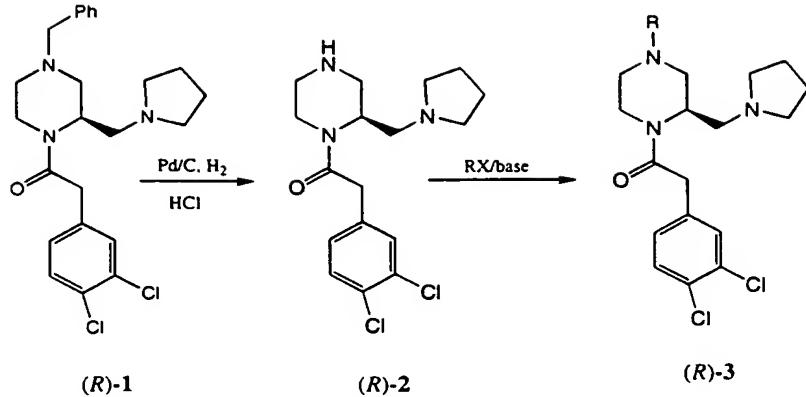
5 (3) Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. A potent new class of k-Receptor agonist: 4-substituted 1-(arylacetyl)-2-[(dialkylamino)methyl] piperazines. *J. Med. Chem.* 1993, 36, 2075-2083.

10 (2S,5S)-Methyl 2-(Hydroxymethyl)-5-[(1-pyrrolidinyl)methyl]-1- piperazine carboxylate(**8**): A solution of **7** (0.25g, 0.571mmol) in ethanol (200 mL) was hydrogenated over 10% palladium on carbon (Degussa type E101 NE/W) at 50 psi for 7 days. Then, filtered through celite and filtrate was evaporated. (0.13 g, 0.5 mmol: 87% yield).

15 (2S,5S)-Methyl 4-[(3,4 - Dichlorophenyl)acetyl]-2-(hydroxy)methyl - 5-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate(**9**): To a solution of 1,1'- carbonyldiimidazole (0.20 g, 1.26 mmol) in dichloromethane (10 mL) was added portionwise 3,4 -dichlorophenylacetic acid (0.25 g, 1.26 mmol) and the resulting solution stirred under nitrogen for 1 Hr, at room temperature. A solution of **8** (0.13g, 0.5 mmol) in dichloromethane (10 mL) was added and the mixture at room temperature for 18 Hr. The reaction mixture was washed with sodium carbonate solution (2 N, 2 x 10 mL), dried, and evaporated to give a viscous oil. This material 20 was dissolved in a mixture of tetrahydrofuran (5 mL) and water (5 mL) and treated with lithium hydroxide (42 mg, 1.0 mmol). The reaction mixture was removed, and the aqueous residue was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried and evaporated to give a colorless gum which was purified by flash column chromatography on silica gel, eluting with ethyl acetate-methanol (40:1) to give **9** (155 mg, 70 %) as a colorless foam.

25 Utilizing the above-denoted intermediates, the following compounds were prepared.

Chiral Compounds



5

Example 1

(R)-4-(Phenylmethyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride [(R)-1 HCl]

10 The compound **(R)-1 HCl** was prepared following the literature procedure³ in 54% yield; mp 168-170°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.65 (4H, m), 1.95-3.00 (6H, m), 3.10-3.80 (9H, m), 4.35 (1H, m), 4.70 (1H, m), 7.00 (1H, m), 7.30 (7H, m); MS (FAB) 448 (M + H)⁺; Anal. Calcd for C₂₄H₂₉Cl₂N₃O·2HCl·H₂O: C, 53.64; H, 6.19; N, 7.82. Found: C, 53.69; H, 5.88; N, 7.49.

15

Example 2

(R)-1-[(3,4-Dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine hydrochloride [(R)-2HCl]

20 The compound was prepared by the catalytic hydrogenation of **(R)-1 HCl** following the procedure described in the above reference. The product was isolated as a free base as clear oil in 81% yield and the dihydrochloride salt was prepared from 1M etherial HCl; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.67 (4H, m), 1.95-3.10 (6H, m), 3.10-3.80 (7H, m), 4.30 (1H, m), 4.65 (1H, m), 7.05 (1H, m), 7.35 (3H, m); MS (FAB) 356 (M + H)⁺.

25

Example 3**(R)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride [(R)-3a HCl]**

5 To the solution of **(R)-2** (712 mg, 2mmol in 10 ml CH₂Cl₂), methanesulfonyl chloride (573 mg, 5 mmol) and pyridine (1ml) were added at 0 °C, stirred overnight at that temperature, the solution was washed with aq. 5% K₂CO₃ solution, extracted with dichloromethane, dried and evaporated solvent to give crude oil. This material was purified by flash column chromatography on silica gel, eluting with dichloromethane-methanol-ammonia (100:5:1), to give the free base, 10 which was dissolved into 2 ml of dichloromethane and HCl (3 ml, 1 M in Et₂O) was added to afford a white salt **(R) -3a HCl** (600 mg, 69%): mp 130-132 °C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.61-1.85 (4H, m), 2.38-2.65 (6H, m), 2.72 (3H, s), 2.80-3.06 (2H, m), 3.15-3.36 (1H, m), 3.50-3.96 (4H, m), 4.48-4.93 (1H, m), 7.00-7.10 (1H, m), 7.25-7.40 (2H, m); MS (FAB) 434 (M + H)⁺; Anal. Calcd for C₁₈H₂₅Cl₂N₃O₃S. HCl.0.5 CH₃OH.: C, 45.64; H, 5.59; N, 8.63. Found: 15 C, 45.69; H, 5.58; N, 8.73.

Example 4**(R)-4-t-Butyl-acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine [(R)-3b].**

20 To the solution of **(R)-2** (356 mg, 1mmol in 10 ml acetone), t-butyl bromoacetate (234 mg, 1.2 mmol) and K₂CO₃ (207 mg, 1.5 mmol) were added at 0 °C, stirred overnight at that temperature, the solution was washed with aq. 5% K₂CO₃ solution, extracted with dichloromethane, dried and evaporated solvent to give crude oil. This material was purified by 25 flash column chromatography on silica gel, eluting with dichloromethane-methanol-ammonia (100:5:1), to give **(R)-3b** (329 mg, 70%): ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.36 (9H, s), 1.91-2.37 (7H, m), 2.65-3.13 (7H, m), 3.58-4.20 (6H, m), 5.00 (1H, m), 7.12-7.21 (2H, m), 7.40 (1H, m). The compound was used directly into the following reaction.

Example 5**(R)-4-[(3,4-dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl]-1-piperazineacetic acid dihydrochloride [(R)-3c 2HCl]**

30 Compound **(R)-3b** (329 mg, 0.7 mmol) was dissolved into 5 ml THF/Et₂O (1:1), and HCl (5 ml, 1 M in Et₂O) was added, kept 12hrs to afford a white salt (**R)-3c HCl** (275 mg, 61%): mp

190°C (d). ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.85-2.20 (4H, m), 2.95-4.41 (17H, m), 5.18-5.35 (1H, m), 7.30-7.45 (1H, m), 7.56-7.72 (2H, m); MS (FAB) 414 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_3$. 2 HCl.0.5 H_2O : C, 45.16; H, 5.78; N, 8.32. Found: C, 44.91; H, 5.88; N, 8.56.

5

Example 6

(R)-4- N-t-Boc-D-aspartic acid- β -benzyl ester-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine [(R)-3d]

To the solution of N-t-Boc-D-aspartic acid- β -benzyl ester (646mg, 2 mmol) and HOBr (10 270mg, 2mmol in 10 ml CH_2Cl_2), DCC (413 mg, 2 mmol) was added at 0 °C, stirred 1h at that temperature, (R)-2 (356 mg, 1 mmol in 10 ml CH_2Cl_2) was added, stirred 24 hrs at room temperature, the solution was washed with aq. 5% K_2CO_3 solution, extracted with dichloromethane, dried and evaporated solvent to give crude oil. This material was purified by flash column chromatography on silica gel, eluting with dichloromethane-methanol-ammonia (100:1:1), to give (R)-3d (628 mg, 95%), ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.35 (9H, s), 1.70-1.87 (4H, m), 2.32-3.16 (6H, m), 3.35-4.46 (6H, m), 4.80-5.68 (6H, m), 7.07-7.45 (8H, m). The compound was used directly into the reaction below.

Example 7

(R)-4-Aspartic acid-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine dihydrochloride [(R)-3e 2HCl]

The compound (R)-3d was dissolved into 1 ml of HOAc, and HCl (1 ml, 2N) was added, standing 20 min, then hydrogenated at 1 atm.,10% Pd on carbon at room temperature for 1 h to afford a white salt (R)-3e (430 mg, 91.5%): mp 168 °C (d). ^1H NMR (DMSO-d_6) δ 1.92-2.16 (4H, m), 2.75-5.28 (18H, m), 2.72 (3H, s), 7.31-7.52 (3H, m), 8.45-8.80 (3H, m); MS (FAB) 471 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{Cl}_2\text{N}_4\text{O}_4$. 2 HCl: C, 46.34; H, 5.18; N, 10.29. Found: C, 45.52; H, 6.02; N, 9.73.

30

Example 8

(R)-4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride [(R)-3f HCl]

The compound was prepared as reported in the literature (*J. Med. Chem.* 1993, 36, 2075-35 2083) from (R)-2. the hydrochloride salt was prepared from 1M etherial HCl to afford (R)-3f HCl

in 88% yield; mp 153–155°C; MS (FAB) 398 ($M + H$)⁺. Anal. Calcd for $C_{19}H_{25}Cl_2N_3O_2 \cdot HCl \cdot H_2O$: C, 52.49; H, 6.03; N, 9.66. Found: C, 50.40; H, 6.23; N, 9.28.

Example 9

(R)-4-(Diethoxyphosphonate)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride [(R)-3g HCl]

To a solution of (*R*)-2 (0.178 g, 0.5 mmol) in 10 mL of CH_2Cl_2 was added Et_3N (0.101 g, 1.0 mmol) and diethylchlorophosphonate (0.174 g, 1.0 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 13 h and then poured over aqueous 10% K_2CO_3 . The organic layer was separated, dried over anhydrous Na_2SO_4 , and evaporated to dryness under reduced pressure to give the compound as a yellow oil. The oil was purified on a silica gel column (solvent system: $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}:28\% \text{ NH}_4\text{OH}$, 95:5:2) and converted to hydrochloride salt by usual method to give (*R*)-3g HCl, 0.10 g (38%); mp 168-170°C; ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.20 (6H, t, J = 7.0 Hz), 1.64 (4H, m), 2.30-2.70 (6H, m), 2.85-3.15 (1H, m), 3.45-3.80 (4H, m), 3.60 (2H, brs), 3.98 (4H, m), 4.35 (1H, m), 4.70 (1H, m), 7.00 (1H, m), 7.30 (2H, m); MS (FAB) 492, 494 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{12}\text{H}_{32}\text{Cl}_2\text{N}_3\text{O}_4\text{P}\cdot\text{HCl}\cdot 0.5\text{H}_2\text{O}$: C, 46.90; H, 6.37; N, 7.81. Found: C, 46.66; H, 5.90; N, 8.16.

Example 10

(R)-4-Trifluoroacetyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride [(R)-3h HCl]

To a solution of **(R)-2** (0.356 g, 1.0 mmol) in 10 mL of CH_2Cl_2 was added Et_3N (0.202 g, 2.0 mmol) and trifluoroacetic anhydride (0.42 g, 2.0 mmol) in a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 12h and TLC showed starting material was still present, added another equivalent of trifluoroacetic anhydride and stirring was continued for additional 12 h. The reaction was worked up as above and the hydrochloride salt was prepared as usual to give **(R)-3h HCl**, 0.25 g (50%); mp 145-147°C; ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.60 (4H, m), 2.20-2.75 (6H, m), 3.10 (1H, m), 3.45-3.80 (4H, m), 4.00 (1H, J = 14.0 Hz, d), 4.25 (1H, m), 4.45 (1H, J = 14.0 Hz, d), 4.70 (1H, m), 7.00 (1H, m), 7.28 (2H, m); MS (FAB) 452, 454 ($M + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{Cl}_2\text{F}_3\text{N}_3\text{O}_2 \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 45.85; H, 4.86; N, 8.44. Found: C, 46.26; H, 4.82; N, 8.33.

Example 11(R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl] -1-piperazinecarboxamide hydrochloride [(R)-3i HCl]

5 To a solution of **(R)-2** (0.356 g, 1.0 mmol) in acetic acid (0.186 g, 3.0 mmol) and water was added KOCN (0.244 g, 3.0 mmol) and the reaction mixture was stirred at room temperature for 72 h. An aqueous 10% K_2CO_3 was added to the reaction mixture to bring the pH to near 12.0 and the product was extracted with CH_2Cl_2 , washed with saturated salt solution, dried over anhydrous Na_2SO_4 . The removal of solvent at reduced pressure gave the crude product which was 10 purified on a silica gel column (solvent system: $CH_2Cl_2:CH_3OH:28\% NH_4OH$, 95:5:1) to give the desired product as a white solid. The hydrochloride salt was prepared from 1M ethereal HCl to give **(R)-3i HCl** as a white solid, 0.15 g (31%); 1H NMR (free base, 200 MHz, $CDCl_3$) δ 1.65 (4H, m), 2.10-3.20 (6H, m), 3.40-3.70 (4H, m), 3.95 (2H, m), 4.20 (2H, $J = 14.0$ Hz, d,m), 4.70 (1H, m), 5.35 (2H, bs), 7.00 (1H, m), 7.25 (2H, m); MS (FAB) 399, 401 ($M + H$) $^+$. Anal. Calcd for $C_{18}H_{24}Cl_2N_4O_2 \cdot HCl \cdot H_2O$: 0.125 CH_2Cl_2 : C, 46.88; H, 5.91; N, 12.06. Found: C, 46.66; H, 5.50; N, 11.97.

Example 12(R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl] -1-piperazinecarboxaldehyde hydrochloride [(R)-3j HCl]

20 To a solution of **(R)-2** (0.356 g, 1.0 mmol) in 10 mL of CH_2Cl_2 was added 1.0 mL of methylformate (excess) at 0°C under a nitrogen atmosphere. The reaction mixture was stirred for 24 h and solvent was removed at reduced pressure to give the crude product. The compound was 25 purified on a silica gel column (solvent system: $CH_2Cl_2:CH_3OH:28\% NH_4OH$, 95:5:1) and converted to the hydrochloride salt, **(R)-3j HCl**, 0.10 g (23%); mp 126°C (d); 1H NMR (free base, 200 MHz, $CDCl_3$) δ 1.62 (4H, m), 2.10-3.20 (6H, m), 3.35-3.85 (5H, m), 4.25 (3H, m), 4.60 (1H, m), 7.00 (1H, m), 7.26 (2H, m), 7.90 (1H, s); MS (FAB) 384, 386 ($M + H$) $^+$.

Example 13(R)-4-[(3,4-Dichlorophenyl)acetyl]-3-[(1-pyrrolidinyl)methyl] -1-piperazine-sulfonamide hydrochloride [(R)-3k HCl]

30 To a solution of **(R)-2** (0.356 g, 1.0 mmol) in 5 mL of p-dioxane was added sulfamide⁴ (NH₂SO₂NH₂, 0.96 g, 10 mmol) under a nitrogen atmosphere and the reaction mixture was

heated to reflux for 2 h. The reaction mixture was evaporated to dryness under reduced pressure and the residue was redissolved in CH_2Cl_2 and washed with aqueous 10% K_2CO_3 , saturated salt solution, and dried over anhydrous Na_2SO_4 . The removal of solvent resulted the free base of the product which was purified on a silica gel column (solvent system: $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}:28\%$ 5 NH_4OH , 98:2:1). The hydrochloride salt was prepared from 1M etherial HCl to give (*R*)-3k HCl , 0.10 g (21%); mp 183-185°C; ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.68 (4H, m), 2.30-3.00 (6H, m), 3.15-4.00 (5H, m), 4.15-4.65 (3H, m), 4.85 (1H, m), 7.00 (1H, m), 7.31 (4H, m); MS (FAB) 435 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{17}\text{H}_{24}\text{Cl}_2\text{N}_4\text{O}_3\text{S} \cdot \text{HCl}$: C, 43.28; H, 5.34; N, 11.87. Found: C, 42.90; H, 5.35; N, 11.43.

10

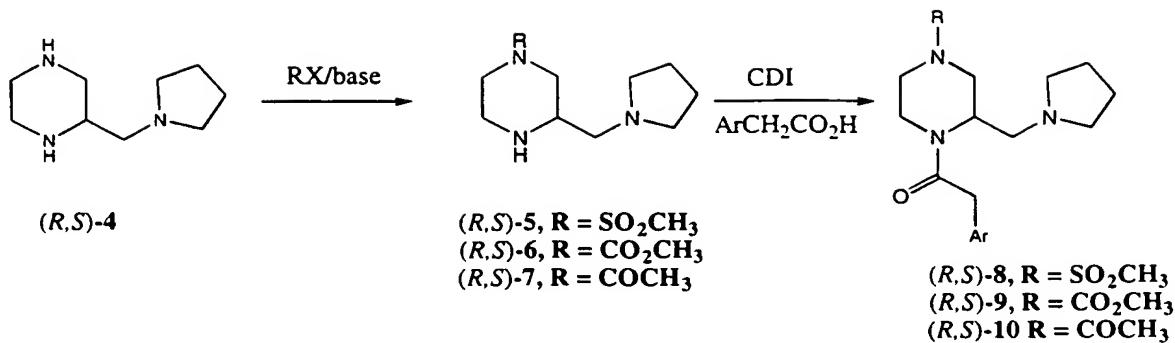
Ref.

(4) Alker, D. et. al. *J. Med. Chem.* 1990, 33, 585.Example 1415 (*R*)-4-(4-Methyphenylsulfonyl)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl] -
piperazine hydrochloride [(*R*)-3l HCl]

To a solution of (*R*)-2 (0.356 g, 1.0 mmol) in 5 mL of CH_2Cl_2 was added p-toluenesulfonyl chloride (0.38 g, 2 mmol) followed by 0.5 mL of pyridine under a nitrogen 20 atmosphere. The reaction mixture was stirred at room temperature for 16 h and then poured onto aqueous 10% K_2CO_3 . The organic layer was separated and dried over anhydrous Na_2SO_4 . The removal of solvent gave the product which was purified on a silica gel column (solvent system: $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}:28\%$ NH_4OH , 98:2:1). The hydrochloride salt was prepared to give (*R*)-3l HCl , 0.15 g (27%); mp 240°C (d); ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.65 (4H, m), 1.95-3.00 (6H, m), 2.38 (3H, s), 3.15-3.85 (5H, m), 4.45 (1H, m), 4.75 (1H, m), 6.95 (1H, m), 7.25 (4H, m), 25 7.50 (2H, $J = 8.0$ Hz, d); MS (FAB) 510 ($\text{M} + \text{H}$) $^+$. Anal. Calcd for $\text{C}_{24}\text{H}_{29}\text{Cl}_2\text{N}_3\text{O}_3\text{S} \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$: C, 52.32; H, 5.35; N, 7.63. Found: C, 52.23; H, 5.50; N, 7.51.

Racemic Compounds

30 Racemic compounds were prepared as illustrated by the following steps.



(R,S)-2-[(1-Pyrrolidinyl)methyl]piperazine hydrochloride [(R,S)-4 HCl]

5 The compound was prepared following the literature procedure¹ and isolated as hydrochloride salt.

10 (R,S)-4-(R= SO₂CH₃, CO₂CH₃, COCH₃)-2-[(1-Pyrrolidinyl)methyl]piperazine hydrochloride [(R,S)-5, 6, 7]

15 These compounds were also prepared according to the procedures described in the literature¹ and each of the products were purified as free base before utilizing below.

Example 15

(R,S)-4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperazine hydrochloride [(R,S)-8a HCl] (General Procedure)

20 1,1'-Carbonyldiimidazole (0.324 g, 2.0 mmol) was added to a stirred solution of 3,4-dichlorophenylacetic acid (0.41 g, 2.0 mmol) in 10 mL of CH₂Cl₂ at room temperature under a nitrogen atmosphere, and the resulting solution was continued stirring for additional 1 h. The resulting solution was then added to a stirred solution of (R,S)-5 (0.247 g, 1.0 mmol) in 10 mL of CH₂Cl₂ at 0°C and the reaction mixture was stirred for further 20 h. The reaction mixture was diluted with CH₂Cl₂ and washed with aqueous 2M Na₂CO₃. The organic layer was dried and evaporated to dryness and the product was purified on a silica gel column (solvent system: CH₂Cl₂:CH₃OH:28% NH₄OH, 98:2:1). The hydrochloride salt was prepared by redissolving the compound in CH₂Cl₂ and treating the solution with 1M etherial HCl to give (R,S)-8a HCl as a

white solid, 0.20 g (32%); NMR (see *R*-3a); MS (FAB) 434 ($M + H$)⁺; Anal. Calcd for $C_{18}H_{25}Cl_2N_3O_3S \cdot HCl \cdot 0.5H_2O$: C, 45.13; H, 5.51; N, 8.77. Found: C, 45.46; H, 5.36; N, 8.71.

The following compounds were similarly prepared from (*R,S*)-5, 6, and 7:

5

Example 16

(*R,S*)-4-Methanesulfonyl-1-[(4-methylsulfonylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride [(*R,S*)-8b HCl]

The compound was prepared from 4-methylsulfonylphenylacetic acid and the hydrochloride salt was recrystallized from CH_3OH to give (*R,S*)-8b HCl in 60% yield; mp 185-188°C; 1H NMR (free base, 200 MHz, $CDCl_3$) δ 1.65 (4H, m), 2.30-2.70 (6H, m), 2.80 (3H, s), 2.85-3.10 (3H, m), 3.00 (2H, m), 3.25 (1H, m), 3.50-3.95 (4H, m), 4.50 (1H, m), 4.80 (1H, m), 7.40 (2H, $J = 7.5$ Hz, d), 7.80 (2H, $J = 7.5$ Hz, d); MS (FAB) 444 ($M + H$)⁺; Anal. Calcd for $C_{19}H_{29}N_3O_5S_2 \cdot HCl$: C, 47.54; H, 6.30; N, 8.75. Found: C, 46.03; H, 6.24; N, 8.80.

15

Example 17

(*R,S*)-4-Methanesulfonyl-1-[(2-nitrophenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride [(*R,S*)-8c HCl]

The compound was prepared from 2-nitrophenylacetic acid in 65% yield as hydrochloride salt; mp 253-255°C; 1H NMR (free base, 200 MHz, $CDCl_3$) δ 1.70 (4H, m), 2.40-3.10 (6H, m), 2.75 (3H, s), 3.45 (1H, m), 3.70-4.00 (4H, m), 4.05-4.30 (2H, m), 4.50 (1H, m), 4.72 (1H, m), 7.45 (3H, m), 8.05 (1H, $J = 8.0$ Hz, d); MS (FAB) 411 ($M + H$)⁺; Anal. Calcd for $C_{18}H_{26}N_4O_5S \cdot HCl$: C, 48.37; H, 6.09; N, 12.54. Found: C, 48.36; H, 5.66; N, 12.29.

25

Example 18

(*R,S*)-4-Methanesulfonyl-1-[(4-trifluoromethylphenyl)acetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride [(*R,S*)-8d HCl]

The compound was prepared as a hydrochloride salt from 4-trifluoromethylphenylacetic acid in 82% yield; 182-185°C; 1H NMR (free base, 200 MHz, $CDCl_3$) δ 1.65 (4H, m), 2.35-3.05 (6H, m), 2.71 (3H, s), 3.25 (1H, m), 3.50-3.95 (5H, m), 4.55 (1H, m), 4.85 (1H, m), 7.30 (2H, m), 7.50 (2H, $J = 7.8$ Hz, d); MS (FAB) 434 ($M + H$)⁺; Anal. Calcd for $C_{19}H_{26}F_3N_3O_3S \cdot HCl \cdot 0.5H_2O$: C, 47.65; H, 5.89; N, 8.77. Found: C, 48.36; H, 5.80; N, 8.51.

35

Example 19**(R,S)-4-Methanesulfonyl-1-[(3-indolylacetyl]-2-[(1-pyrrolidinyl)-methyl]piperazine hydrochloride [(R,S)-8e HCl]**

5 The compound was prepared from 3-indoleacetic acid and isolated as free base in 40% yield and converted to hydrochloride salt; mp 219-221°C; ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.65 (4H, m), 2.10-3.00 (6H, m), 2.55 (3H, s), 3.10-3.45 (2H, m), 3.45-3.90 (4H, m), 4.05 (1H, m), 4.55 (1H, m), 4.90 (1H, m), 7.05 (3H, m), 7.25 (1H, m), 7.50 (1H, m), 8.95 (1H, bs); MS (FAB) 405 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{N}_4\text{O}_3\text{S} \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 58.09; H, 7.07; N, 13.55.

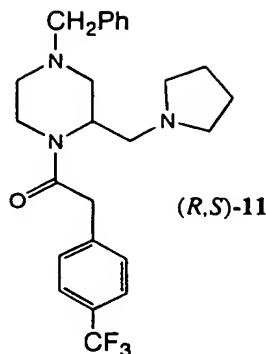
10 Found: C, 58.37; H, 6.68; N, 13.30.

Example 20**(R,S)-Methyl 4-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride [(R,S)-9a HCl]**

15 The compound was prepared from 4-methylsulfonylphenylacetic acid and the hydrochloride was prepared from 1M etherial HCl to give **(R,S)-9a HCl** in 46 % yield; mp 225°C; ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.60 (4H, m), 2.15-2.95 (6H, m), 2.98 (3H, s), 3.15 (2H, m), 3.35 (3H, m), 3.60 (3H, s), 3.95 (2H, m), 4.30 (1H, m), 4.72 (1H, m), 7.45 (2H, m), 20 7.75 (2H, $J = 7.5$ Hz, d); MS (FAB) 424 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{N}_3\text{O}_5\text{S} \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$: C, 51.72; H, 6.62; N, 9.05. Found: C, 51.93; H, 6.47; N, 8.44.

Example 21**(R,S)-Methyl 4-[(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride [(R,S)-9b HCl]**

25 The compound was prepared as a hydrochloride salt from 4-trifluoromethylphenylacetic acid to give **(R,S)-9b HCl** in 48%; mp 210°C; ^1H NMR (200 MHz, CDCl_3) δ 1.50 (4H, m), 1.95-2.30 (6H, m), 2.35-3.50 (4H, m), 3.65 (3H, s), 3.70-4.50 (5H, m), 7.45 (4H, m); MS (FAB) 414 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_3 \cdot \text{HCl} \cdot 0.25\text{H}_2\text{O}$: C, 52.86; H, 6.10; N, 9.25. Found: C, 53.03; H, 5.94; N, 8.94.



Another minor product (*R,S*)-11 was isolated as a hydrochloride salt from this reaction in 10% yield; mp 190°C; MS (FAB) 446 (M + H)⁺.

5

Example 22

(R,S)-Methyl 4-[(3-indolyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride [(R,S)-9c HCl]

10 The compound was prepared from 3-indoleacetic acid and the hydrochloride salt was prepared to give (*R,S*)-9c HCl in 75% yield; mp 143°C; ¹H NMR (200 MHz, CDCl₃) δ 1.55 (4H, m), 1.90-2.52 (6H, m), 2.70-3.75 (9H, m), 3.35 (3H, s), 6.60 (2H, m), 6.85 (2H, m), 7.20 (1H, s), 7.65 (1H, brs); MS (FAB) 385 (M + H)⁺.

15

Example 23

(R,S)-Methyl 4-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride [(R,S)-9d HCl]

20 The compound was prepared from 2-nitrophenyacetic acid and hydrochloride was prepared from 1M etherial HCl to give (*R,S*)-9d HCl in 42% yield; mp 228°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.60 (4H, brs), 1.80-2.30 (4H, m), 2.70 (2H, m), 3.05 (2H, m), 3.60 (3H, s), 3.55-4.10 (4H, m), 4.35 (2H, J = 14.0 Hz, dd), 5.10 (1H, m), 7.50 (3H, m), 8.05 (1H, J = 7.5 Hz, d); MS (FAB) 391 (M + H)⁺; Anal. Calcd for C₁₉H₂₆N₄O₅.HCl: C, 53.46; H, 6.37; N, 13.12. Found: C, 54.29; H, 6.38; N, 12.58.

25

Example 24**(R,S)-Methyl 4-[(2-methoxyphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate hydrochloride [(R,S)-9e HCl]**

5 The compound was prepared as above from 2-methoxyphenylacetic acid to give **(R,S)-9e HCl** in 12% yield; mp 120°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.65 (4H, m), 2.25 -2.95 (6H, m), 3.10 (1H, m), 3.30-4.10 (5H, m), 3.60 (3H, s), 3.70 (3H, s), 4.40 (1H, m), 4.70 (1H, m), 6.84 (2H, m), 7.15 (3H, m); MS (FAB) 376 (M + H)⁺; Anal. Calcd for C₂₀H₂₉N₃O₄.HCl.H₂O: C, 55.87; H, 7.50; N, 9.77. Found: C, 55.78; H, 6.97; N, 9.42.

10

Example 25**(R,S)-Methyl 4-[(2-aminophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-1-piperazine-carboxylate dihydrochloride [(R,S)-9f 2HCl]**

15 The compound was prepared by the hydrogenation of **(R,S)-9e HCl** on 10% Pd/C following the procedure described in the literature¹. The compound, **(R,S)-9f 2HCl**, was isolated as dihydrochloride in 84% yield; mp 195°C (d); ¹H NMR (200 MHz, DMSO-d₆) δ 2.00 (4H, m), 3.05-4.45 (16H, m), 3.75 (3H, s), 5.00 (1H, m), 7.45 (4H, brs); MS (FAB) 361 (M + H)⁺; Anal. Calcd for C₁₉H₂₈N₄O₃.2HCl.H₂O: C, 50.56; H, 7.15; N, 12.41. Found: C, 50.36; H, 7.26; N, 20 12.05.

Example 26**(R,S)-4-Acetyl-1-[(4-methylsulfonylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]-piperazine hydrochloride [(R,S)-10a HCl]**

25

The compound was prepared as above from 4-methylsulfonylphenylacetic acid and the hydrochloride salt was prepared in usual fashion to give **(R,S)-10a HCl** in 45% yield; mp 145-147°C; ¹H NMR (200 MHz, DMSO-d₆) δ 1.90 (4H, m), 2.17 (3H, s), 2.65-3.80 (6H, m), 3.32 (3H, s), 3.85-4.45 (8H, m), 5.05 (1H, m), 7.65 (2H, J = 8.0 Hz, d), 7.95 (2H, J = 8.0 Hz, d); MS (FAB) 408 (M + H)⁺.

Example 27**(R,S)-4-Acetyl-1-(4-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride [(R,S)-10b HCl]**

5 The compound was prepared from 4-trifluoromethylphenylacetic acid and isolated as hydrochloride salt, **(R,S)-10b HCl**, in 30% yield; mp 110°C; ¹H NMR (200 MHz, DMSO-d₆) δ 2.00 (4H, m), 2.15 (3H, s), 2.70-3.25 (6H, m), 3.50-4.45 (8H, m), 5.05 (1H, m), 7.70 (4H, m); MS (FAB) 398 (M + H)⁺.

Example 28**(R,S)-4-Acetyl-1-[(2-trifluoromethylphenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazinecarboxylate hydrochloride [(R,S)-10c HCl]**

10 The compound was prepared from 2-trifluoromethylphenylacetic acid and the hydrochloride salt was made from 1M etherial HCl to give **(R,S)-10c HCl** in 57%; 220°C (d); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.65 (4H, m), 2.05 (3H, s), 2.25-3.25 (6H, m), 3.40-4.10 (6H, m), 4.50 (2H, m), 4.70 (1H, m), 7.30 (2H, m), 7.60 (2H, m); MS (FAB) 398 (M + H)⁺.

Example 29**(R,S)-4-Acetyl-1-[(3-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride [(R,S)-10d HCl]**

20 The compound was prepared from 3-nitrophenylacetic acid and the hydrochloride salt, **(R,S)-10d HCl** was isolated as a white solid in 69% yield; mp 143-145°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.63 (4H, brs), 2.05 (3H, s), 2.20-2.80 (6H, m), 2.90-3.25 (2H, m), 3.50-3.90 (3H, m), 4.00 (1H, J = 14.0 Hz, d), 4.45 (2H, m), 4.65 (1H, m), 7.45 (2H, m), 8.00 (2H, m); MS (FAB) 375 (M + H)⁺; Anal. Calcd for C₁₉H₂₆N₄O₄.HCl.H₂O: C, 53.21; H, 6.81; N, 13.06. Found: C, 53.51; H, 6.13; N, 12.91.

Example 30**(R,S)-4-Acetyl-1-[(2-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-carboxylate hydrochloride [(R,S)-10e HCl]**

30 The compound was prepared as above from 2-nitrophenylacetic acid to give **(R,S)-10e HCl** as white solid in 50% yield; mp 180°C (d); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.63 (4H, m), 2.04 (3H, s), 2.20-2.85 (6H, m), 2.98-3.35 (3H, m), 3.60-4.25 (4H, m), 4.60 (2H, m),

7.35 (3H, m), 8.00 (1H, J = 7.0 Hz, d); MS (FAB) 375 ($M + H$)⁺; Anal. Calcd for $C_{19}H_{26}N_4O_4 \cdot HCl \cdot 0.5H_2O$: C, 55.54; H, 6.62; N, 13.64. Found: C, 54.38; H, 6.35; N, 13.58.

Example 31

**(R,S)-4-Acetyl-1-[(4-nitrophenyl)acetyl]-3-[(1-pyrrolidinyl)-methyl]piperazine-
carboxylate hydrochloride [(R,S)-10f HCl]**

The compound was prepared from 2-nitrophenylacetic acid as before to give (*R,S*)-10f HCl in 52% yield; 146-148°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.68 (4H, m), 2.07 (3H, s), 2.20-2.75 (6H, m), 3.40-3.90 (3H, m), 4.05 (1H, J = 13.5 Hz, d), 4.50 (2H, m), 7.35 (2H, J = 8.0 Hz, d), 8.10 (2H, J = 8.0 Hz, d); MS (FAB) 375 (M + H)⁺; Anal. Calcd for C₁₉H₂₆N₄O₄·HCl·0.5H₂O·0.125CH₂Cl₂: C, 53.36; 6.61; 13.01. Found: C, 53.16; H, 6.27; N, 13.36.

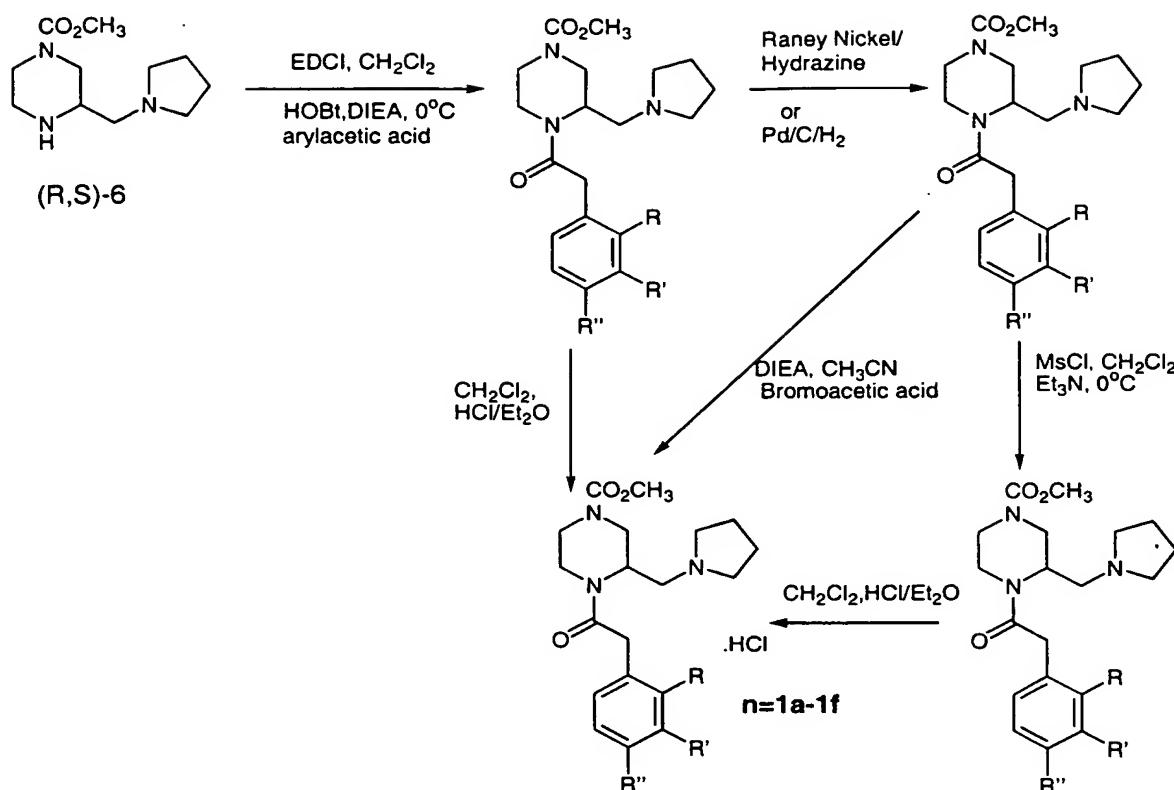
Example 32

(R,S)-4-(Phenylmethyl)-1-[(4,5-dichloro-2-nitrophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]piperazine dihydrochloride [(R,S)-12-2HCl]

The compound was prepared from 4-phenylmethyl-2[(1-pyrrolidinyl)methyl]piperazine (Ref. 1) and 4,5-dichloro-2-nitrophenylacetic acid following the method described above to give **(R,S)-12 2HCl** in 63% yield; mp 235°C (d); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.66 (4H, m), 2.05-3.00 (8H, m), 3.45 (4H, m), 4.00 (5H, m), 4.60 (1H, m), 7.35 (6H, m), 8.15 (1H, s); MS (FAB) 493 (M + H)⁺; Anal. Calcd for C₂₄H₂₉Cl₂N₄O₃.2HCl: C, 50.99; 5.53; 9.91. Found: C, 50.55; H, 5.16; N, 9.44.

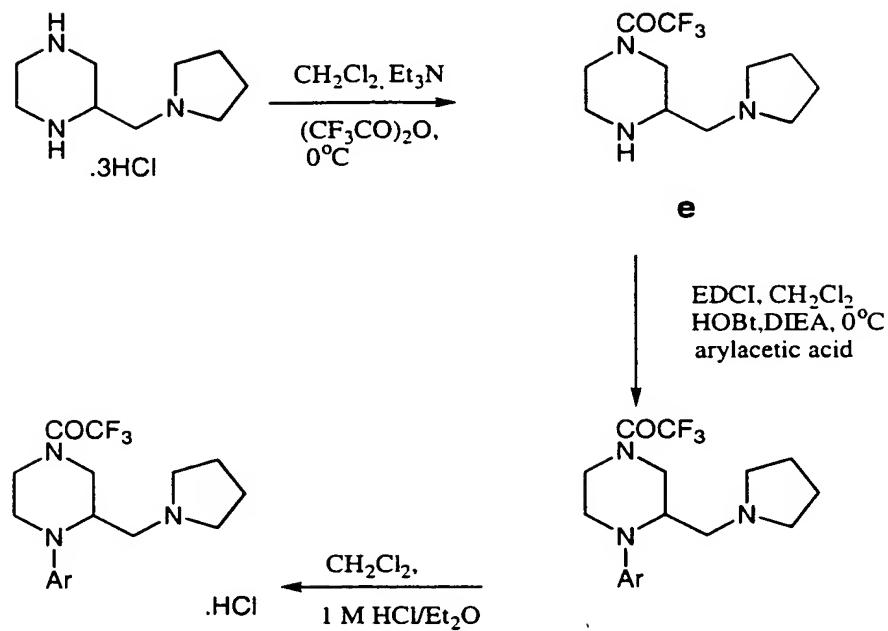
25 The preparation of compounds of formula IA (compounds 1a through 1qq) follow
according to Schemes A, B, C, D, E and F.

Scheme A



Compound 1a: R = $-\text{NHCH}_2\text{CO}_2\text{H}$, R' = H, R'' = CF_3
 Compound 1b: R = $-\text{NMs}_2$, R' = H, R'' = CF_3
 Compound 1c: R = $-\text{NHMs}$, R' = H, R'' = H
 Compound 1d: R = $-\text{NMs}_2$, R' = H, R'' = H
 Compound 1e: R = $-\text{SO}_2\text{NHCH}_3$, R' = H, R'' = H
 Compound 1f: R = -H, R' = H, R'' = $-\text{SO}_2\text{NHCH}_3$

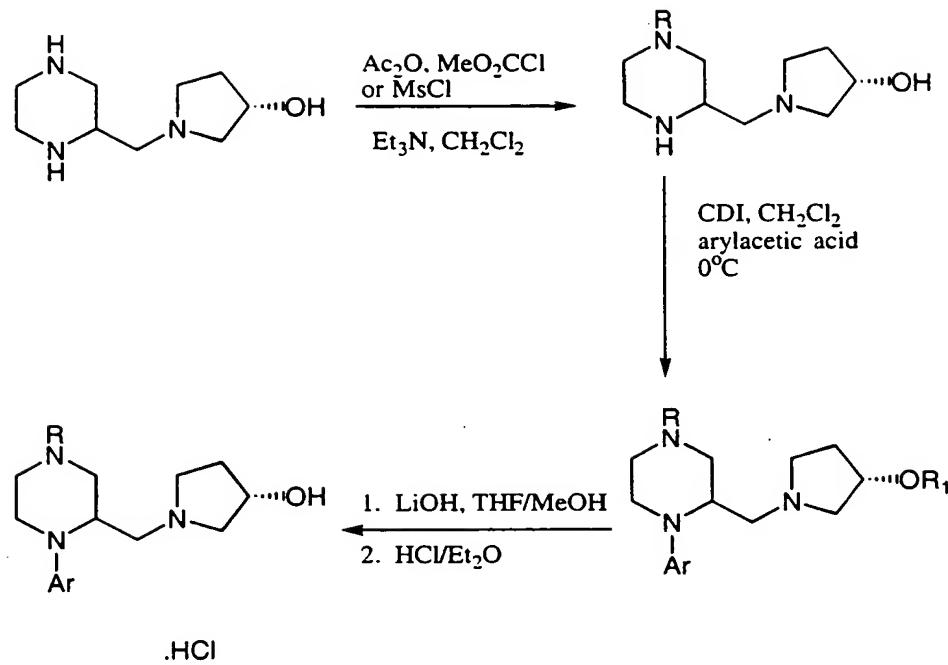
Scheme B



Compound 1g : Ar = -trans-3-furanacyrlyl

Compound 1h : Ar = -4-trifluoromethylphenyl acetyl

Scheme C



1III: R= -Ms, Ar= -3,4-dichlorophenylacetyl

1nn: R= -Ms, Ar= -4-trifluorophenylacetyl

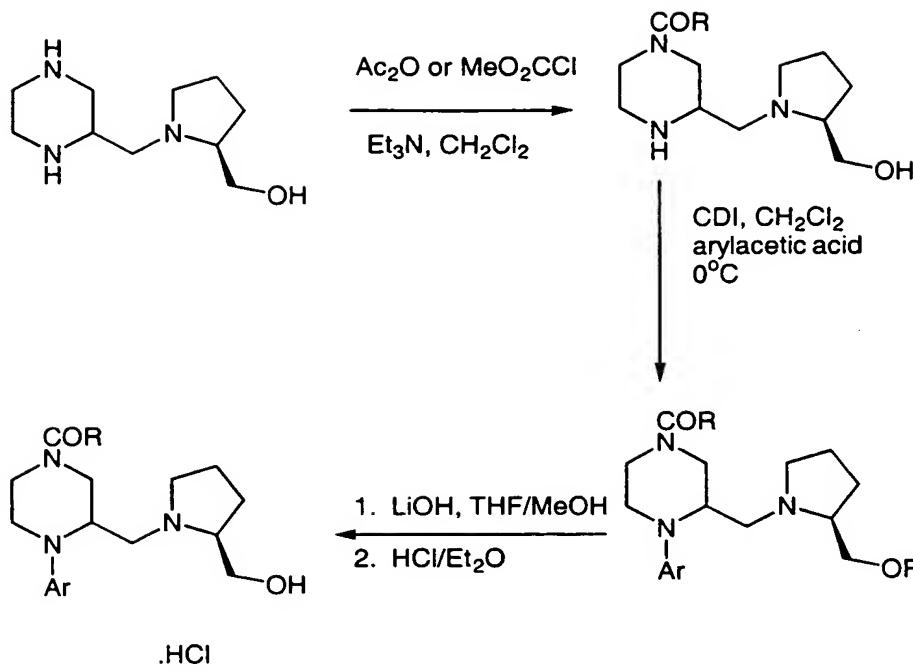
1j: R= -CO₂CH₃,

R₁=Ar= -4-trifluorophenylacetyl

1u: R=COCH₃,

R₁=Ar=4-methylsulphonyl phenylacetyl

Scheme D



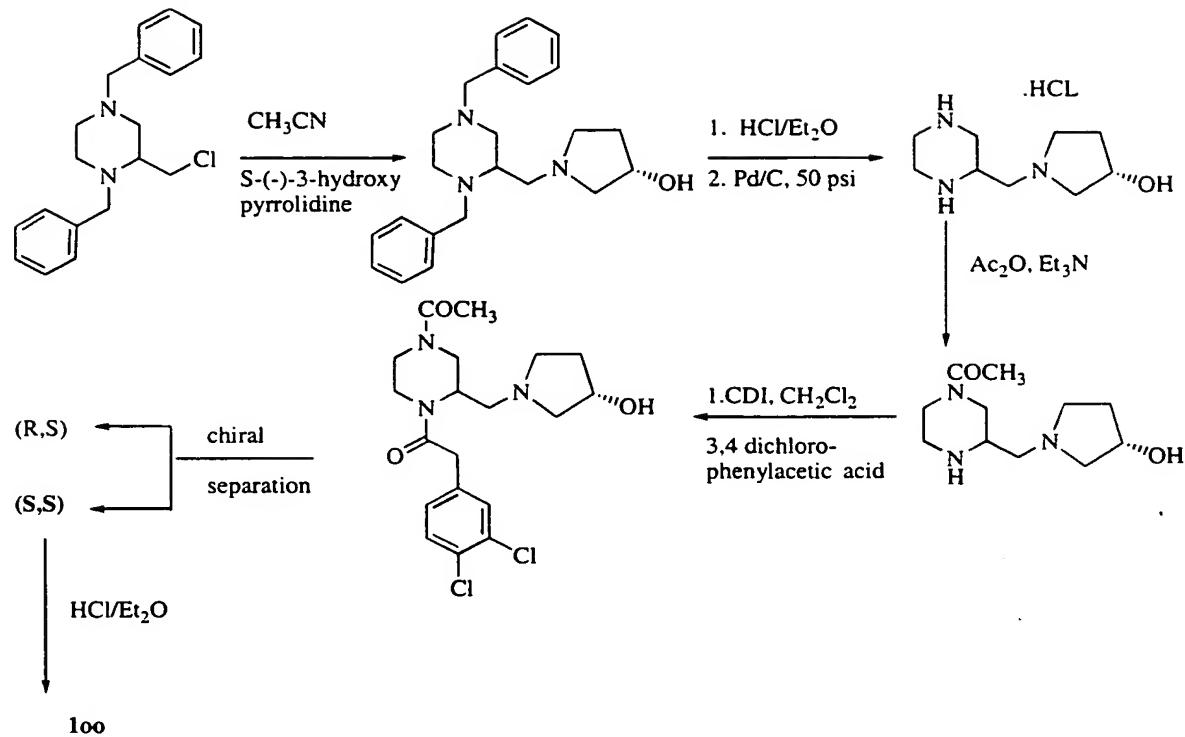
1I: $\text{R}=\text{CO}_2\text{CH}_3$,
 $\text{Ar}=3,4\text{-dichlorophenylacetyl}$

1bb: $\text{R}=\text{COCH}_3$,
 $\text{Ar}=4\text{-methylsulphonylphenylacetyl}$

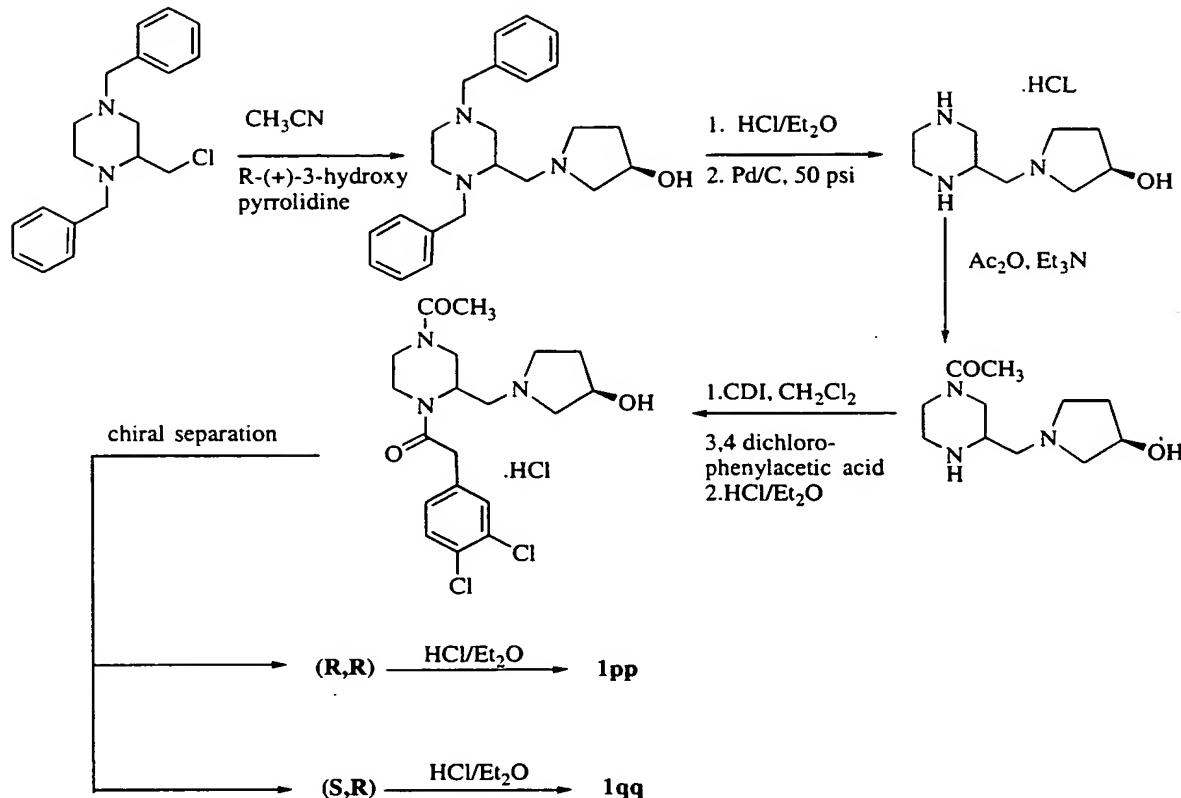
1k: $\text{R}=\text{CO}_2\text{CH}_3$,
 $\text{R}_1=\text{Ar}=3,4\text{-dichlorophenylacetyl}$

1aa: $\text{R}=\text{COCH}_3$,
 $\text{R}_1=\text{Ar}=4\text{-methylsulphonylphenylacetyl}$

Scheme E



Scheme F

**Example 1a**

Methyl-4-[2-glycyl-4-(trifluoromethylphenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate

5

Methyl-4-[(2-nitro-4-trifluoromethylphenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate¹ (Procedure A) (a): To a solution of 2-nitro-4-trifluorophenylacetic acid (2.8 g, 11.2 mmol) in 30 mL of dry CH₂Cl₂ under a nitrogen atmosphere was added HOBr (1.3 g., 9.6 mmol). The reaction mixture is stirred at 0°C and added solid EDCI (2.25 g, 11.75 mmol). Then, stirred for 30 minutes at 0°C. A solution of methyl-3-(R,S)-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate¹ (2.0 g, 8.78 mmol) in 5 mL of dry CH₂Cl₂ was added followed by DIEA (1.68 mL, 9.64 mmol). The reaction mixture was stirred for 24 h while warming to room temperature. The reaction mixture was then poured into water (50 mL) and stirred for 30 minutes. After dilution with CH₂Cl₂, the organic layer was separated, washed with saturated NaHCO₃, salt solution, and water. Then, dried over Mg₂SO₄. The

compound was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂:CH₃OH:(98:2) to give the desired product as a free base(3.15 g, 78% yield). Then, proceed on to the next step. ¹H NMR (free base 200MHz, CDCl₃) δ 1.76 (4H, m), 2.65 (4H, m), 3.02 (2H, m), 3.74 (s, 3H), 4.21 (4H, m), 7.56 (dd, J=2.4, 8.0 Hz, 1H), 7.85 (d, J= 8.0 Hz, 1H), 8.4 (d, J=2.4 Hz, 1H); MS(FAB) m/z 459.

Methyl-4-[(2-amino-4-trifluoromethylphenyl)acetyl]-3-(R,S)-[(1pyrrolidinyl)-methyl]-1-piperazinecarboxylate hydrochloride (b): Compound a (1.18 gm, 2.57 mmol) was dissolved in ethanol (50 mL) and heated to 55⁰C. Hydrazine hydrate(0.9 mL, 28.12 mmol) and 1 scoop of Raney Nickel was added to the reaction flask. Stir vigorously. Continue to add the 10 Raney Nickel until all of the hydrazine is consumed (when the bubbling has stopped). Cool to 30⁰C and filter through celite and wash with hot methanol. (Do not allow the Raney nickel to become dry!). Evaporate the solvent and generate an HCl salt(1.0 gm; 90.6%); m.p. 160-165⁰C. ¹H NMR (free base 200MHz, CDCl₃) δ 1.76 (4H, m), 2.5-3.1 (7H, m), 3.74 (3H, s), 4.15 (2H, m), 4.55 (2H, m), 6.90 (1H, J=2.4 Hz, d), 6.95 (1H, J= 2.4, 8.0 Hz, dd), 7.15 (1H, J=8.0 Hz, d). MS 15 (FAB) m/z 429. Anal. Calc. For C₂₀H₂₇N₄F₃O₃.HCl.H₂O: C, 49.69; H, 6.21; N, 11.60. Found: C, 49.57; H, 6.04; N, 11.32.

To a solution of bromoacetic acid(0.356 g, 2.56 mmol) and DIEA(1.0 mL, 5.74 mmol) in CH₃CN(15 mL) was added compound b and heated to 55⁰C for 16 hr. Then, heated to 75⁰C for 4 hr. The reaction was complete. Evaporate the solvent and re-dissolve in ethanol(25.0 mL). 20 Add 0.1 M Na₂CO₃ (20 mL) and filter and wash with boiling ethanol (15 mL). Evaporate the filtrate and dissolve in isopropanol (10 mL). Add diethyl ether (5.0 mL) until precipitate forms. Filtered. A white solid is obtained(m.p. 165-170⁰C; 0.3 g, 24.8 % yield). ¹H NMR (free base 200MHz, CDCl₃) δ 2.19(4H, m), 2.95 (4H, m), 3.2-3.7 (4H,m), 3.74 (3H, s), 3.8-4.2 (4H, m), 4.7 (1H, m), 5.2 (1H, m), 6.86 (1H, J=2.4 Hz, d), 7.0 (2H, J=8.0 Hz, d). MS (FAB) m/z 487. Anal. 25 Calc. For C₂₂H₂₉N₄F₃O₅.0.5 C₂H₆O. 0.5H₂O: C, 53.28; H, 6.37; N, 10.81. Found: C, 53.50; H, 6.25; N, 10.51.

Example 1b**Methyl-4-[(2-[N,N-bis-methylsulfonamido]-4-trifluoromethyphenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl)-methyl]-1-piperazinecarboxylate dihydrochloride**

5 To a solution of compound b (0.4 g, 0.933 mmol) and triethylamine(0.26 mL, 1.86 mmol) in CH₂Cl₂(10.0 mL) at 0°C was added methanesulfonyl chloride(0.144 mL, 1.86 mmol). The reaction was stirred for 16 hr. The reaction was diluted with CH₂Cl₂(40.0 mL), washed with saturated NaHCO₃ solution and water. Then, dried over Mg₂SO₄. Then, isolated on a silica gel column (solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (98:2:2) to give the desired product as a 10 free base (0.4 g, 73 %). Evaporate the solvent and generate an HCl salt(0.14 gm; m.p. 155-160°C). ¹H NMR (free base 200MHz, CDCl₃) δ 1.76 (4H, m), 2.75-3.31 (11H, m), 3.47 (3H, s), 3.50 (3H, s), 3.72 (3H, s), 3.8-4.3(5H, m), 4.55 (1H, m), 4.95 (1H, m), 7.5-7.9(3H, Ar). MS (FAB) m/z 585. Anal. Calc. For C₂₂H₃₁N₄F₃O₇S₂·2HCl: C, 42.54; H, 5.19; N, 9.02. Found: C, 42.58; H, 5.23; N, 8.91.

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Example 1c**Methyl-4-[(2-[N-methylsulfonamido]phenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate hydrochloride**

20 **Methyl-4-[(2-nitro-phenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (c):** The compound was prepared from 2-nitro-phenylacetic acid following Procedure A and isolated on a silica gel column (solvent system: CH₂Cl₂: CH₃OH:28% NH₄OH (99:1:2) to give the desired product as a free base (3.15 g, 78 %). Then, proceed on to the next step.. ¹H NMR (free base 300MHz, CDCl₃) d 1.75 (4H, m), 2.53 (4H, m), 3.02 (2H, m), 3.74 (s, 3H), 4.21 (4H, m), 7.4 (1H, ArH, m) 7.56 (1H, J=1.2Hz, d), 7.61 (1H, J=1.2, 7.4Hz, dd), 8.11 (1H, J=8.0Hz, d).

25 **Methyl-4-[(2-amino-phenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl)methyl]-1-piperazinecarboxylate (d):** Then, compound c was dissolved in ethanol(200 mL) and Pd/C (Degussa; 10%; 3.0 g) were added into a Parr bottle (500 mL). Then, the bottle was attached to a 30 Parr Shaker Hydrogenator at 50 psi for 6 hr. The reaction was complete. This was filtered through celite. Evaporate the solvent and proceed on to the final step.

Then, to a solution of the above compound d (0.15 g, 0.33 mmol) and triethylamine(0.10 mL, 0.66 mmol) in CH₂Cl₂(10.0 mL) at 0°C was added methanesulfonyl chloride(0.026 mL, 0.33 mmol). The reaction was stirred for 16 hr. The reaction was diluted

with CH_2Cl_2 (20.0 mL), washed with saturated NaHCO_3 solution and water. Then, dried over Mg_2SO_4 . Then, isolated on a silica gel column (solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (98:2:2) to give the desired product as a free base (0.1 g, 68 %). Evaporate the solvent and generate an HCl salt(0.06gm; m.p. 130-135 ^0C). ^1H NMR (free base 200MHz, CDCl_3) δ 1.75 (4H, m), 2.2 (1H, m), 2.5-3.1 (6H, m), 3.01 (3H, s), 3.50 (2H, m), 3.73 (3H, s), 3.8-4.5 (5H, m), 5.02 (1H, m), 6.88-7.55 (3H, Ar). MS (FAB) m/z 439. Anal. Calc. For $\text{C}_{20}\text{H}_{30}\text{N}_4\text{O}_5\text{S}_2\text{HCl}$: C, 50.57; H, 6.58; N, 11.79. Found: C, 50.55; H, 6.64; N, 11.36.

Example 1d

10 Methyl-4-[(2-[N,N-bis-methylsulfonamido]phenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl) methyl]-1-piperazinecarboxylate hydrochloride

To a solution of the compound d (0.70 g, 1.94 mmol) and triethylamine(0.44 mL, 3.19 mmol) in CH_2Cl_2 (10.0 mL) at 0 ^0C was added methanesulfonyl chloride(0.247 mL, 3.19 mmol). 15 The reaction was stirred for 16 hr. The reaction was diluted with CH_2Cl_2 (20.0 mL), washed with saturated NaHCO_3 solution and water. Then, dried over Mg_2SO_4 . Then, isolated on a silica gel column (solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (98:2:2) to give the desired product as a free base (0.7 g, 70 %). Evaporate the solvent and generate an HCl salt(0.75 g; m.p. 145-150 ^0C). ^1H NMR (free base 200MHz, CDCl_3) δ 1.76 (4H, m), 2.2 (1H, m), 2.5-3.1 (6H, m), 3.44 (3H, s), 3.49 (3H, s), 3.71 (3H, s), 3.8-4.5 (5H, m), 4.50 (1H, m), 4.89 (1H, m), 7.23-7.75 (3H, Ar). MS (FAB) m/z 517. Anal. Calc. For $\text{C}_{21}\text{H}_{32}\text{N}_4\text{O}_7\text{S}_2\text{HCl}$: C, 46.05; H, 6.22; N, 10.09. Found: C, 45.60; H, 6.01; N, 10.13.

Example 1e

25 Methyl-4-[(2-[N-methylamino)sulfamyl]phenyl)acetyl]-3-(R,S)-[(1-pyrrolidinyl) methyl]-1-piperazinecarboxylate hydrochloride

The compound was prepared from (N-methylamino)sulfamyl phenyl acetic acid (a mixture of the ortho and para isomer) following Procedure A and isolated on a silica gel column [solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (99:2:1): R_f = 0.56] to give the desired product as a free base (0.70g, 70 %). Then, generate the HCl salt(m.p. 155-160 ^0C ; 0.31 g). ^1H NMR (free base 200MHz, CDCl_3) δ 1.75 (m,4H), 2.53 (m,4H), 2.66 (d, J =5.2 Hz, 3H), 2.82 (m, 3H), 3.25 (m, 1H), 3.72 (s, 3H), 3.84 (m, 2H), 4.15 (m, 2H), 4.50 (m, 1H), 4.85 (m, 1H), 7.45 (dd, J = 4.0, 8.2

Hz, 2H) 7.79 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 8.2 Hz, 1H); MS(FAB) m/z 439. Anal. Calc. For C₂₀ H₃₀ N₄ O₅ S.HCl: C, 50.13; H, 6.61; N, 11.36. Found: C, 50.57; H, 6.58; N, 11.79.

Example 1f

5 **Methyl-4-[-4-[N-methylamino)sulfamyl]phenyl]acetyl]-3-(R,S)-[(1-pyrrolidinyl) methyl]-1-piperazinecarboxylate hydrochloride**

The compound was isolated from the above reaction on a silica gel column [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (99:1:2) : R_f = 0.62] to give the desired product as a free base. Then, generate the HCl salt (m.p. 135-140°C; 6.0 mg). ¹H NMR (free base 200MHz, CDCl₃) δ 1.74 (m, 4H), 2.53 (m, 4H), 2.66 (d, J=5.2 Hz, 3H), 2.82 (m, 3H), 3.25 (m, 1H), 3.71 (s, 3H), 3.84 (m, 2H), 4.15 (m, 2H), 4.50 (m, 1H), 4.85 (m, 1H), 7.48 (m, 2H, ArH) 7.73 (m, 2H, ArH); MS(FAB) m/z 439. Anal. Calc. For C₂₀ H₃₀ N₄ O₅ S.HCl: C, 50.13; H, 6.61; N, 11.36. Found: C, 50.57; H, 6.58; N, 11.7.

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Example 1g

4-Trifluoroacetyl-1-[(trans-3-furanacyrlate]-2-(R,S)-(1-pyrrolidinyl)methyl] piperazine hydrochloride

20 4-Trifluoroacetyl-2-(R,S)-(1-pyrrolidinyl)methyl piperazine(e): To a solution of (R,S)-2-(1-pyrrolidinyl)methyl piperazine hydrochloride (1.0 g, 3.58 mmol) and Et₃N (0.5 mL, 3.58 mmol) in 10 mL of CH₂Cl₂ was added trifluoroacetic anhydride (0.5 mL, 3.58 mmol) at 0°C. The reaction mixture is stirred at 0°C for 5 h. The reaction mixture was evaporated under reduced pressure (due to the water solubility of this compound there was no aqueous work-up) and isolated on a silica gel column (solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (98:2:2) to give the desired product as a free base (0.18 g, 20 %); ¹H NMR (free base 200MHz, CDCl₃) δ 1.76 (m, 4H), 2.25-3.15 (m, 10H), 3.26 (t, 2H), 3.88 (m, 1H), 4.39 (t, 1H).

25 To a solution of trans-3-furanacyrlic acid (0.10 g, 0.74 mmol) in 5 mL of dry CH₂Cl₂ under a nitrogen atmosphere was added HOBt (0.10 g, 0.74 mmol). The reaction mixture is stirred at 0°C and added solid EDCI (0.143 g, 0.75 mmol). Then, stirred for 30 minutes at 0°C. A solution of compound e (0.18 g, 0.67 mmol) in 5 mL of dry CH₂Cl₂ was added followed by DIEA (0.177 mL, 1.01 mmol). The reaction mixture was stirred for 24 h while warming to room temperature. The reaction mixture was then poured into water (50 mL) and stirred for 30 minutes. After dilution with CH₂Cl₂, the organic layer was separated, washed with saturated

NaHCO₃, salt solution, and water. Then, dried over Mg₂SO₄. The compound was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂:CH₃OH:28% NH₄OH(99:1:2) to give the desired product as a free base(m.p. 144-145°C; 0.25 g, 95% yield). The hydrochloride salt was prepared from 1M ethereal HCl.(0.1 g) ¹H NMR (free base 200MHz, CDCl₃) δ 1.74 (m, 4H), 2.57 (m, 5H), 3.11 (m, 2H), 3.31 (m, 2H), 4.05 (m, 1H), 4.25 (m, 1H), 4.50 (m, 1H), 4.65 (m, 1H), 6.58 (d, J = 3.3, 7.8 Hz, 2H), 7.44 (m, 1H), 7.64 (d, J=3.3Hz, 2H); MS (FAB) m/z 386; Anal. Calcd. For C₁₈ H₂₂ N₃ F₃ O₃.HCl: C, 51.25; H, 5.50; N, 9.96. Found: C, 51.44; H, 5.57; N, 9.86.

10 **Example 1h**
4-Trifluoroacetyl-1-[(4-trifluoromethylphenyl)acetyl]-2-(R,S)-(1-pyrrolidinyl) methyl piperazine hydrochloride

To a solution of 4-trifluoromethyl-phenyl acetic acid (0.08g, 0.39 mmol) in CH₂Cl₂ (5.0 mL) was added 1,1' carbonyldiimidazole (0.06 g, 0.39 mmol) under a nitrogen atmosphere and stirred for 1 h. Cool to 0°C and compound e (0.1 g, 0.39 mmol) in CH₂Cl₂ (5.0 mL) was added. Then, stirred for 16 h and the reaction mixture was then poured into a solution of ice-cold saturated NaHCO₃ and stirred for 30 minutes. After dilution with CH₂Cl₂, the organic layer was separated, washed with saturated salt solution, and dried over Mg₂SO₄. The compound was purified by flash column chromatography on silica gel, eluting with CH₂Cl₂:CH₃OH:28% NH₄OH(99:1:2) to give the desired product as a free base(m.p. 140-145 °C;0.08 g, 47% yield). The hydrochloride salt was prepared from 1M ethereal HCl.(0.05 g) ¹H NMR (free base 200MHz, CDCl₃) δ 1.75 (m, 4H), 2.55 (m, 5H), 2.69-3.2 (m, 4H), 3.8 (m, 1H), 3.83 (m, 2H), 4.50 (m, 1H), 4.65 (m, 1H), 7.38 (d, J = 7.7 Hz, 2H), 7.64 (d, J= 7.8 Hz, 2H); MS (FAB) m/z 452; Anal. Calcd. For C₂₀ H₂₃ N₃ F₃ O₂.HCl.0.3Et₂O: C, 49.96; H, 5.30; N, 8.24. Found: C, 49.62; H, 5.16; N, 7.84.

30 **Example 1i**
Methyl-4-[(3,4-dichlorophenyl)acetyl]-3-(R,S)-[(4'-methylpiperazinecarboxylate)methyl]-1-piperazinecarboxylate hydrochloride

The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with methyl-3 (R,S)-[(4'-methylpiperazinecarboxylate)methyl]-1-piperazinecarboxylate; mp: (HCl salt)160-165°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.5-1.8 (2H, m), 2.2-3.2 (8H, m), 3.3-3.5 (5H,

5 m), 3.6 (3H, s), 3.7 (3H, s), 3.9-4.5 (3H, m), 4.7-4.8 (1H, m), 7.1 (1H, m), 7.4 (2H, m); MS (FAB) 487 (M + H)⁺; Anal. Calcd. for C₂₁H₂₈Cl₂N₄O₅.HCl. H₂O: C, 46.55; H, 5.77; N, 10.34. Found: C, 46.02; H, 5.93; N, 10.91.

10 **Example 1j**

Methyl-4-[(4-a,a,a-trifluoromethylphenyl)acetyl]-3-(R,S)-
[3-(S)-(4'- α , α , α -trifluoro methylphenylacetate)-1-(pyrrolidinyl)methyl]-1-
piperazinecarboxylate hydrochloride (1j)

15 The compound was prepared by coupling of 4- α , α , α -trifluoromethylphenyl- acetic acid with methyl-3-(R,S)-[3-(S)-hydroxy-1-(pyrrolidinyl)methyl]-1-piperazine carboxylate; mp: (HCl salt)98-100°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.6-3.1 (11H, m), 3.4-5.4 (12H, m), 7.1-7.7 (8H, m); MS (FAB) 616 (M + H)⁺; Anal. Calcd for C₂₉H₃₁F₆N₃O₅.HCl. H₂O.0.25NH₄Cl: C, 50.97; H, 5.16; N, 6.66. Found: C, 50.45; H, 5.07; N, 6.67.

20

Example 1k

Methyl-4-[(3,4-dichlorophenyl)acetyl]-3-(R,S)-
[(2-(S)-pyrrolidinemethyl-3',4'-dichlorophenyl acetate)methyl]-1-piperazinecarboxylate
hydrochloride

25

The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with methyl-3-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]-1-piperazinecarboxylate; mp: (HCl salt)77-80°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.3-2.0 (5H, m), 2.0-2.5 (4H, m), 2.5-3.3 (5H, m), 3.7 (3H, s), 3.4-4.8 (3H, m), 3.8-4.9 (5H, m), 7.0 (2H, m), 7.3 (4H, m); MS (FAB) 632 (M + H)⁺; Anal. Calcd for C₃₀H₃₃F₆N₃O₄.

30

Example 1l

Methyl-4-[(3,4-dichlorophenyl)acetyl]-3-(R)-[(2-(S)-pyrrolidinemethanol)methyl]-1-
piperazinecarboxylate hydrochloride

35

The compound was prepared by aq. LiOH hydrolyzation of **1k**; mp: (HCl salt)135-138°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.6-1.8 (4H, m), 3.7 (3H, s), 2.0-4.1 (15H, m), 4.3-4.8 (2H, m), 7.0 (1H, m), 7.3 (1H, m); MS (FAB) 444 (M + H)⁺; Anal. Calcd. for C₂₀H₂₇Cl₂N₃O₄.HCl. H₂O: C, 48.16; H, 6.06; N, 8.42. Found: C, 48.64; H, 6.05; N, 8.45.

Example 1mMethyl-4-[(2-nitro-4- α,α,α -trifluoromethylphenyl)acetyl]-3-(R,S)-[(2-(S)-pyrrolidine methanol)methyl]-1-piperazinecarboxylate hydrochloride

5 The compound was prepared by aq. LiOH hydrolysis of methyl-4-[(2-nitro-4- α,α,α -trifluoromethylphenyl)acetyl]-3-(R,S)-[(2-(S)-pyrrolidine methanol)-2'-nitro-4'- α,α,α -trifluoromethylphenylacetate)methyl]-1-piperazinecarboxylate; mp: (HCl salt) 136-140°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.6-1.9 (3H, m), 3.7 (3H, d), 2.1-3.6 (12H, m), 3.9-4.9 (6H, m), 7.4 (1H, d), 7.8 (1H, d), 8.3 (1H, s); MS (FAB) 489 ($M + H$) $^+$; Anal. Calcd. for

10 $\text{C}_{21}\text{H}_{27}\text{F}_3\text{N}_3\text{O}_6\text{HCl}$: C, 48.05; H, 5.38; N, 10.67. Found: C, 47.81; H, 5.27; N, 10.49.

Example 1nMethyl-4-[(4-methylsulphonylphenyl)acetyl]-3-(R,S)-[(2-(S)-pyrrolidinemethyl-4'-methylsulphonylphenylacetate)methyl]-1-piperazinecarboxylate hydrochloride

15 The compound was prepared by coupling of 4-methylsulphonylphenylacetic acid with methyl-3-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]-1-piperazinecarboxylate; mp: (HCl salt) 133-135°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.4-2.5 (5H, m), 3.0 (3H, s), 2.6-3.3 (8H, m), 3.4-4.9 (15H, m), 7.4 (4H, m), 7.9 (4H, m); MS (FAB) 650 ($M + H$) $^+$; Anal. Calcd. for

20 $\text{C}_{30}\text{H}_{39}\text{S}_2\text{N}_3\text{O}_9\text{HCl} \cdot 0.75\text{NH}_4\text{Cl}$: C, 49.61; H, 5.97; N, 7.23. Found: C, 50.07; H, 6.17; N, 7.26.

Example 1oMethyl-4-[(4-methylsulphonylphenyl)acetyl]-3-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]-1-piperazinecarboxylate hydrochloride

25 The compound was prepared by aq. LiOH hydrolysis of compound 1n; mp: (HCl salt) 130-135°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.6-1.9 (4H, m), 2.1-2.5 (2H, m), 2.5-3.4 (7H, m), 3.0 (3H, s), 3.4-4.2 (6H, m), 3.7 (3H, m), 4.2-5.0 (2H, m), 7.5 (2H, m), 7.9 (2H, m); MS (FAB) 454 ($M + H$) $^+$; Anal. Calcd. for $\text{C}_{21}\text{H}_{31}\text{SN}_3\text{O}_6\text{HCl.H}_2\text{O}$: C, 49.65; H, 6.75; N, 8.27.

30 Found: C, 50.19; H, 6.77; N, 8.26.

Example 1pMethyl-4-[(2-amino-4- α,α,α -trifluoromethylphenyl)acetyl]-3-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]-1-piperazinecarboxylate hydrochloride

35 The compound was prepared by Pd catalyzed hydrogenation of compound 1m; mp: (HCl salt) 140-143°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.7-3.3 (12H, m), 3.7 (3H, s), 3.3-4.3

$\text{C}_{21}\text{H}_{29}\text{F}_3\text{N}_4\text{O}_4 \cdot 2\text{HCl} \cdot \text{CH}_3\text{OH}$: C, 46.90; H, 6.26; N, 9.94. Found: C, 46.96; H, 6.14; N, 9.93.

Example 1q

Methyl-4-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[3-(S)-
(3',4'-dichlorophenyl acetate)-1-(pyrrolidinyl)methyl]-1-piperazinecarboxylate
hydrochloride

The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with methyl-3-(R,S)-[3-(S)-hydroxy-1-(pyrrolidinyl)methyl]-1-piperazine carboxylate; mp: (HCl salt) 125-128°C; ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.9-3.1 (9H, m), 3.4-3.8 (8H, m), 4.0-4.2 (3H, m), 4.5-5.2 (3H, m), 7.1 (2H, m), 7.4 (4H, m); MS (FAB) 618 ($\text{M} + \text{H}$) $^+$; Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{Cl}_4\text{N}_3\text{O}_5\text{HCl}$: C, 49.60; H, 4.62; N, 6.43. Found: C, 49.39; H, 4.65; N, 6.44.

Example 1r

4-Acetyl-1-[3-(N-methylsulfonamido)phenyl]acetyl-2-(R,S)-[(1-pyrrolidinyl) methyl]piperazine hydrochloride

The compound was prepared by methylsulphonylation of 4-acetyl-1-[3-amino)phenyl]acetyl-2-(*R,S*)-[(1-pyrrolidinyl) methyl]piperazine as clear oil, the dihydrochloride salt was prepared from 1M etherial HCl; mp: (HCl salt) 140°C(dec.); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.5-1.7 (4H, m), 1.8-3.1 (13H, m), 3.4-4.9 (9H, m), 6.5 (2H, m), 7.0 (2H, m); MS (FAB) 423 (M + H)⁺. Anal. Calcd. for C₂₀H₃₀N₄O₄S.HCl. NH₄Cl: C, 46.87; H, 6.88; N, 13.67. Found: C, 44.83; H, 7.18; N, 13.16.

Example 1s

4-Acetyl-1-[(2-acetylaminophenyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl] piperazine hydrochloride

30 The compound was prepared by acetylation of 4-acetyl-1-[(2-aminophenyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl]piperazine; mp: (HCl salt) 173°C (dec.); ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.3-1.8 (6H, m), 2.0 (3H, s), 2.1 (3H, s), 2.2-3.4 (8H, m), 3.6-4.8 (6H, m), 6.9-7.2 (3H, m), 7.8 (1H, m); MS (FAB) 387 ($\text{M} + \text{H}$) $^+$; Anal. Calcd. for $\text{C}_{21}\text{H}_{30}\text{N}_4\text{O}_3 \cdot \text{HCl} \cdot 2\text{H}_2\text{O}$: C, 54.95; H, 7.69; N, 12.21. Found: C, 54.53; H, 6.91; N, 11.92.

Example 1t4-Acetyl-1-[(4-acetylaminophenyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl] piperazine hydrochloride

5 The compound was prepared by acetylation of 4-acetyl-1-[(4-aminophenyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl]piperazine; mp: (HCl salt)165°C(dec.); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.5-1.7 (5H, m), 1.9-2.1 (6H, m), 2.2-3.1 (8H, m), 3.5-4.7 (6H, m), 7.0 (2H, m), 7.4 (2H, m); MS (FAB) 387 (M + H)⁺; Anal. Calcd for C₂₁H₃₀O₃N₄.HCl. H₂O: C, 57.20; H, 7.54; N, 12.71. Found: C, 57.05; H, 7.31; N, 12.74.

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Example 1u4-Acetyl-1-[(4-methylsulfonyl)phenyl]acetyl]-2-(R,S)-[3-(S)-(4'-methylsulfonyl phenyl acetate)-1-(pyrrolidinyl)methyl] piperazine hydrochloride

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The compound was prepared by coupling of 4-methylsulfonylphenylacetic acid with 4-acetyl-2-(R,S)-[3-(S)-hydroxy-1-(pyrrolidinyl)methyl] piperazine; mp: (HCl salt)160-163°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.7-2.2 (7H, m), 2.3-3.2 (12H, m), 3.0 (6H, s), 3.5-4.1 (8H, m), 4.4-5.2 (4H, m), 7.4 (4H, m), 7.8 (4H, m); MS (FAB) 620(M + H)⁺; Anal. Calcd for C₂₉H₃₇S₂N₃O₈.HCl: C, 53.00; H, 5.98; N, 6.39. Found: C, 52.26; H, 6.00; N, 6.37.

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Example 1v4-Acetyl-1-[(4- α , α , α -trifluoromethylphenyl)acetyl]-2-(R,S)-[3-(S)-(4'- α , α , α trifluoro methylphenyl acetate)-1-(pyrrolidinyl)methyl] piperazine hydrochloride

25

The compound was prepared by coupling of 4- α , α , α -trifluoromethylphenyl acetic acid with 4-acetyl-2-(R,S)-[3-(S)-hydroxy-1-(pyrrolidinyl)methyl] piperazine; mp: (HCl salt)134-136°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.6-3.2 (15H, m), 3.4-4.1 (5H, m), 4.3-5.2 (3H, m), 7.3 (4H, m), 7.5 (4H, m); MS (FAB) 599 (M + H)⁺; Anal. Calcd for C₂₉H₃₁F₆N₃O₄.HCl. 0.5NH₄Cl: C, 52.55; H, 5.17; N, 7.40. Found: C, 52.05; H, 5.56; N, 7.90.

30

Example 1w4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[3-(S)-(3',4'-dichlorophenyl acetate)-1-(pyrrolidinyl)methyl]piperazine hydrochloride

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The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-acetyl-2-(R,S)-[3-(S)-hydroxy-1-(pyrrolidinyl)methyl] piperazine; mp: (HCl salt)122-125°C; ¹H NMR

(free base, 200 MHz, CDCl_3) δ 1.6-1.9 (3H, m), 2.1 (3H, s), 2.1-3.9 (14H, m), 4.0-5.3 (3H, m), 7.1 (2H, m), 7.4 (4H, m); MS (FAB) 602 ($M + H$) $^+$; Anal. Calcd for $\text{C}_{27}\text{H}_{29}\text{Cl}_4\text{N}_3\text{O}_4\text{.HCl}$: C, 50.84; H, 4.74; N, 6.59. Found: C, 49.33; H, 4.76; N, 6.85.

5

Example 1x

4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[(2-(S)-pyrrolidinemethyl-3',4' dichlorophenylacetate)methyl]piperazine hydrochloride

10 The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-acetyl-2-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]piperazine; mp: (HCl salt) 107-110°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.5-2.0 (3H, m), 2.0-2.2 (3H, d), 2.2-3.3 (9H, m), 3.5-4.1 (8H, m), 4.4-4.9 (2H, m), 7.1 (2H, m), 7.4 (4H, m); MS (FAB) 616 ($M + H$) $^+$; Anal. Calcd. for $\text{C}_{28}\text{H}_{31}\text{Cl}_4\text{N}_3\text{O}_4\text{.HCl}$. NH_4Cl : C, 47.68; H, 5.14; N, 7.94. Found: C, 47.80; H, 5.38; N, 9.05.

15

Example 1y

4-Acetyl-1-[(4-trifluoromethylphenyl)acetyl]-2-(R,S)-[2-(S)-pyrrolidinemethyl-4'-trifluoromethylphenylacetate)methyl]piperazine hydrochloride

20 The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-acetyl-2-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]piperazine; mp: (HCl salt) 110-113°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.5-3.3 (12H, m), 2.1 (3H, s), 3.5-4.1 (9H, m), 4.3-4.9 (1H, m), 7.3 (4H, m), 7.5 (4H, m); MS (FAB) 614 ($M + H$) $^+$; Anal. Calcd for $\text{C}_{30}\text{H}_{33}\text{F}_6\text{N}_3\text{O}_4\text{.HCl.0.5NH}_4\text{Cl}$: C, 53.24; H, 5.36; N, 7.24. Found: C, 53.86; H, 5.45; N, 6.91.

25

Example 1z

4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[(2-(S)-pyrrolidine methanol) methyl]piperazine hydrochloride

30 The compound was prepared by aq. LiOH hydrolyzation of compound 1x; mp: (HCl salt) 123-125°C; ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.6-2.0 (4H, m), 2.1 (3H, m), 2.2-3.4 (10H, m), 3.4-4.0 (5H, m), 4.4-5.0 (2H, m), 7.1 (2H, m), 7.4 (2H, m); MS (FAB) 428 ($M + H$) $^+$; Anal. Calcd. for $\text{C}_{20}\text{H}_{27}\text{Cl}_2\text{N}_3\text{O}_3\text{.HCl}$: C, 51.68; H, 6.07; N, 9.04. Found: C, 49.84; H, 6.08; N, 9.03.

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Example 1aa4-Acetyl-1-[(4-methylsulphonylphenyl)acetyl]-2-(R,S)-[(2-(S)-pyrrolidinemethyl-4'-methylsulphonylphenylacetate)methyl]piperazine hydrochloride

5 The compound was prepared by coupling of 4-methylsulphonylphenylacetic acid with 4-acetyl-2-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]piperazine; mp: (HCl salt) 145-148°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.5-2.0 (3H, m), 2.1 (3H, m), 3.0 (6H, s), 2.5-3.3 (9H, m), 3.6-4.2 (9H, m), 4.5 (1H, m), 7.5 (4H, m), 7.9 (4H, m); MS (FAB) 634 (M + H)⁺; Anal. Calcd. for C₃₀H₃₉S₂N₃O₈.HCl.0.25NH₄Cl: C, 52.71; H, 6.05; N, 6.66. Found: C, 52.02; H, 6.19; N, 6.59

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Example 1bb4-Acetyl-1-[(4-methylsulphonylphenyl)acetyl]-2-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]piperazine hydrochloride

15 The compound was prepared by aq. LiOH hydrolysis of compound 1aa; mp: (HCl salt) 138-140°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.6-2.0 (4H, m), 2.1 (3H, m), 2.2-3.0 (5H, m), 3.1 (3H, s), 3.1-4.0 (10H, m), 4.4-5.0 (2H, m), 7.5 (2H, m), 7.9 (2H, m); MS (FAB) 438 (M + H)⁺; Anal. Calcd. for C₂₁H₃₁SN₃O₅.HCl.H₂O: C, 51.26; H, 6.96; N, 8.54. Found: C, 50.36; H, 6.92; N, 8.90.

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Example 1cc4-Acetyl-1-[(4-trifluoromethylphenyl)acetyl]-2-(R,S)-[(2-(S)-pyrrolidinemethanol)methyl]piperazine hydrochloride

25 The compound was prepared by aq. LiOH hydrolysis of compound 1y; mp: (HCl salt) 123-125°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.6-2.2 (4H, m), 2.1 (3H, s), 2.2-4.0 (15H, m), 4.5-5.0 (2H, m), 7.4 (2H, m), 7.6 (2H, m); MS (FAB) 428 (M + H)⁺; Anal. Calcd for C₂₁H₂₈F₃N₃O₃.HCl.NH₄Cl: C, 48.75; H, 6.43; N, 10.83. Found: C, 47.46; H, 6.04; N, 12.40.

30

Example 1dd4-Formyl-1-[(2-N-methylsulfamylphenyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl]piperazine hydrochloride

35 The compound was prepared by coupling of 2-(N-methylaminosulfonyl)phenyl acetic acid with 4-formyl-2-(R,S)-[(1-pyrrolidinyl)methyl] piperazine; mp: (HCl salt) 150°C (dec.); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.7 (4H, m), 2.2-3.2 (11H, m), 3.4-4.0 (4H, m), 4.2-5.4 (4H, m),

7.0 (1H, m), 7.4 (2H, m), 7.6 (1H,), 8.0 (1H, m); MS (FAB) 409 (M + H)⁺; Anal. Calcd for C₁₉H₂₈O₄N₄S.HCl. 0.5NH₄Cl: C, 48.38; H, 6.62; N, 13.36. Found: C, 48.08; H, 6.46; N, 13.33.

Example 1ee

4-Carbonylimidazole-1-[(3,4-dichlorophenyl)acetyl]-2-(R)-[(1-pyrrolidinyl)methyl]piperazine hydrochloride

The compound was prepared by coupling of 1,1'-carbonyldiimidazole with 1-[(3,4-dichlorophenyl)acetyl]-2-(R)-[(1-pyrrolidinyl)methyl] piperazine; mp: (HCl salt) 148°C (dec.); ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.5-1.7 (4H, m), 2.1-2.5 (5H, m), 2.6-3.4 (4H, m), 3.5-4.8 (7H, m), 6.9-7.4 (4H, m), 8.0 (1H, m); MS (FAB) 450 (M + H)⁺; Anal. Calcd for C₂₁H₂₅Cl₂N₅O₂.2HCl. H₂O: C, 46.60; H, 5.40; N, 12.94. Found: C, 45.41; H, 5.33; N, 12.73.

Example 1ff

4-Allyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R)-[(1-pyrrolidinyl)methyl]piperazine hydrochloride

The compound was prepared by coupling of allyl bromide with 1-[(3,4-dichlorophenyl)acetyl]-2-(R)-[(1-pyrrolidinyl)methyl] piperazine in 81% yield; mp: (HCl salt) 157-160°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.4-2.0 (6H, m), 2.3-3.0 (6H, m), 3.1-3.8 (4H, m), 4.3-4.8 (1H, m), 4.9-5.1 (2H, m), 5.7-5.9 (1H, m), 7.0-7.3 (3H, m); MS (FAB) 396 (M + H)⁺; Anal. Calcd for C₂₀H₂₇Cl₂N₃O.2HCl: C, 51.19; H, 6.23; N, 8.95. Found: C, 50.89; H, 6.42; N, 8.65.

Example 1gg

4-Acetyl-1-[(2-pyridyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl]piperazine hydrochloride

The compound was prepared by coupling of 2-pyridylacetic acid with 4-acetyl-2-(R,S)-[(1-pyrrolidinyl)methyl] piperazine; mp: (HCl salt) 127-130°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.4-1.7 (4H, m), 2.0 (3H, s), 2.2-3.2 (9H, m), 3.4-4.8 (6H, m), 6.8-7.5 (3H, m), 8.4 (1H, m); MS (FAB) 331 (M + H)⁺; Anal. Calcd. for C₁₈H₂₆N₄O₂.2HCl. 0.5NH₄Cl: C, 50.27; H, 7.03; N, 14.65. Found: C, 50.86; H, 6.47; N, 15.79.

Example 1hh4-Formyl-1-[(2-pyridyl)acetyl]-2-(R,S)-[(1-pyrrolidinyl)methyl]piperazine hydrochloride

5 The compound was prepared by coupling of 2-pyridinylacetic acid with 4-formyl-2-(R,S)-[(1-pyrrolidinyl)methyl]piperazine; mp: (HCl salt) 125-128°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.5-1.7 (4H, m), 2.1-3.6 (10H, m), 3.7-4.9 (5H, m), 6.9-7.3 (2H, m), 7.6 (1H, m), 8.0 (1H, m), 8.6 (1H, m); MS (FAB) 317 (M + H)⁺; Anal. Calcd. for C₁₇H₂₄N₄O₂.2HCl.NH₄Cl: C, 46.11; H, 6.83; N, 15.82. Found: C, 46.37; H, 6.51; N, 16.35.

10

Example 1iiMethyl-4-[(3,4-dichlorophenyl)acetyl]-3-(S)-[(2-(S)-pyrrolidinemethanol)methyl]-1-piperazinecarboxlate hydrochloride

15 The compound was prepared by aq. LiOH hydrolyzation of **1k**; mp: (HCl salt) 137-140°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 1.5-2.0 (4H, m), 3.7 (3H, s), 2.1-3.7 (14H, m), 3.8-4.9 (3H, m), 7.1 (1H, m), 7.3 (2H, m); MS (FAB) 444 (M + H)⁺; Anal. Calcd. for C₂₀H₂₇Cl₂N₃O₄.HCl. 0.5NH₄Cl: C, 47.33; H, 5.96; N, 9.66. Found: C, 47.55; H, 6.11; N, 9.39.

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Example 1jj4-Methanesulfonyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[3-(S)-methanesulfonate-1-(pyrrolidinyl) methyl]piperazine hydrochloride

25 The compound was prepared from 1-[(3,4-dichlorophenyl)acetyl]-2-[(3-hydroxy-1-pyrrolidinyl)methyl]piperazine dihydrochloride¹ (0.25 g, 0.56 mmol), methanesulfonyl chloride (0.43 mL, 5.56 mmol), triethylamine (2.3 mL, 16.53 mmol) and CH₂Cl₂ (20 mL) at 0°C for 6 h. After dilution with saturated NaHCO₃ solution (20 mL) and washed with water (20mL). Then, dried over Mg₂SO₄. The compound was purified by flash chromatography on silica gel, eluting with CH₂Cl₂:CH₃OH:28%NH₄OH(99:1:2) to give the desired product as a free base (0.28 g; 94% yield) and a hydrochloride salt was generated(0.067 g; m.p. 130-132°C; ¹H NMR (free base, 300 MHz, CDCl₃) δ 2.10(m, 1H), 2.29(m, 1H), 2.59(m, 4H), 2.89 (s. 3H), 3.01 (s, 3H), 3.2-3.5(m, 2H), 3.60-3.9(m, 4H), 4.90 (m, 1H), 5.15(m, 1H), 7.12(d, J=8.2 Hz, 1H), 7.43 (d, J= 8.3Hz, 2H); MS (FAB) 528 (M + H)⁺; Anal. Calcd. for C₁₉H₂₇Cl₂N₃O₆S₂.HCl: C, 40.40; H, 5.00; N, 7.44. Found: C, 40.29; H, 5.07; N, 7.04.

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Example 1kk4-Methylsulphonyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[3-(S)-(3',4'dichlorophenyl acetate)-1-(pyrrolidinyl)methyl]piperazine hydrochloride

5 The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-methylsulphonyl-2-(R,S)-[3-(S)-(hydroxy)-1-(pyrrolidinyl)methyl]piperazine; mp: (HCl salt) 145-148°C; ¹H NMR (freebase, 200 MHz, CDCl₃) δ 1.5-1.9 (2H, m), 2.2-3.0 (7H, m), 2.7 (3H, s), 3.5-4.0 (8H, m), 4.9-5.2 (3H, m), 7.1 (2H, m), 7.4 (4H, m); MS (FAB) 638(M + H)+; Anal. Calcd. for C₂₆H₂₉Cl₄N₃O₅S. HCl. 0.5NH₄Cl: C, 44.52; H, 4.60; N, 7.00. Found: C, 45.66; H, 4.72; N, 10 7.61.

Example 1ll4-Methylsulphonyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R,S)-[3-(S)-hydroxy-1-pyrrolidinyl] methyl]piperazine hydrochloride

15 The compound was prepared by aq. LiOH hydrolyzation of 1kk; mp: (HCl salt) 150-153°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.5-2.3(4H, m), 2.4-3.2 (7H, m), 2.8 (3H, s), 3.4-4.0 (5H, m), 4.5-5.2 (3H, m), 7.1(1H, m), 7.4 (2H, m); MS (FAB) 450 (M + H)+; Anal. Calcd. For C₁₈H₂₅Cl₂N₃O₄S. HCl. 0.25NH₄Cl: C, 43.22; H, 5.44; N, 9.10. Found: C, 43.23; H, 5.16; N, 20 9.8

Example 1mm4-Methylsulphonyl-1-[(4- α , α , α -trifluoromethylphenyl)acetyl]-2-(R,S)-[3-(S)-(4'- α , α , α -trifluoro methylphenyl acetate)-1-(pyrrolidinyl)methyl]piperazine hydrochloride

25 The compound was prepared by coupling of 4-(a,a,a-trifluoromethyl)phenyl acetic acid with 4-methyl sulphonyl-2-(R,S)-[3-(S)-hydroxy-1-(pyrrolidinyl) methyl] piperazine; mp: (HCl salt) 120-123°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.8-2.2 (4H, m), 2.4-3.3 (8H, m), 2.7 (3H, s), 3.6-4.0 (6H, m), 4.8-5.2 (2H, m), 7.4 (4H, m), 7.6 (4H, m); MS (FAB) 636 (M + H)+; Anal. Calcd. For C₂₈H₃₁F₆N₃O₅S. HCl: C, 50.04; H, 4.80; N, 6.25. Found: C, 50.34; H, 4.80; N, 6.09.

Example 1nn4-Methylsulphonyl-1-[(4- α,α,α -trifluoromethylphenyl)acetyl]-2-(R,S)-[(3-(S)-hydroxy-1-pyrrolidinyl)methyl] piperazine hydrochloride

5 The compound was prepared by aq. LiOH hydrolyzation of 1mm; mp: (HCl salt) 145°C(dec.); ^1H NMR (free base, 200 MHz, CDCl_3) δ 1.5-2.1 (3H, m), 2.3-3.4 (9H, m), 2.8 (3H, s), 3.7-4.0 (5H, m), 4.3-5.0 (2H, m), 7.4 (2H, m), 7.6 (2H, m); MS (FAB) 450 ($M + H$) $^+$; Anal. Calcd. for $\text{C}_{19}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_4\text{S}$. HCl: C, 46.96; H, 5.60; N, 8.65. Found: C, 46.45; H, 5.66; N, 8.69.

Example 1oo4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-(S)-[(3'-(S)-hydroxy-1-pyrrolidine)methyl]piperazine hydrochloride

10 The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-acetyl-15 2-(R,S)-[(3'-(S)-hydroxypyrrolidine)methyl]piperazine. Then, this racemic mixture was separated on a Chiralpak AD column using 100% acetonitrile as the eluant. Then, from the 2-(S), 3'-(S) enantiomer a HCl salt was generated (1.0 gm.); mp: (HCl salt) 130-135°C; $[\alpha]^{20} +25.56^\circ$ (0.85%; w/v MeOH). ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.74 (1H, m), 2.13 (3H, s), 2.2(1H, m), 2.3-3.2 (10H, m), 3.45-3.71 (3H, m), 4.11 (1H, d) 4.21-4.74(2H, m), 4.55((1H, m), 20 7.10 (1H, $J = 8.25$ Hz, d), 7.41 (2H, $J = 8.28$ Hz, d); MS (FAB) 414 ($M + H$) $^+$; Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_3\text{HCl}$.0.5 H_2O : C, 49.65; H, 5.77; N, 8.91. Found: C, 49.58; H, 5.65; N, 9.13.

Example 1pp4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-(R)-[(3'-(R)-hydroxy-1-pyrrolidine)methyl]piperazine hydrochloride

25 The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-acetyl-2-(R,S)-[(3'-(R)-hydroxy-1-pyrrolidine)methyl]piperazine. Then, this racemic mixture was separated on a Chiralpak AD column using 100% acetonitrile as the eluant. Then, from the 2-30 (R), 3'-(R) enantiomer a HCl salt was generated (0.9 gm.); mp: (HCl salt) 130-135°C; $[\alpha]^{20} -30.49^\circ$ (0.88%; w/v MeOH). ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.74 (1H, m), 2.13 (3H, s), 2.2(1H, m), 2.3-3.2 (10H, m), 3.45-3.71 (3H, m), 4.11 (1H, d) 4.21-4.74(2H, m), 4.55((1H, m), 7.10 (1H, $J = 8.25$ Hz, d), 7.41 (2H, $J = 8.28$ Hz, d); MS (FAB) 414 ($M + H$) $^+$; Anal. Calcd. for $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_3\text{HCl}$: C, 50.62; H, 5.81; N, 9.32. Found: C, 49.94; H, 5.84; N, 8.97.

Example 1qq
4-Acetyl-1-[(3,4-dichlorophenyl)acetyl]-2-(S)-
[(3'-(R)-hydroxy-1-pyrrolidine)methyl]piperazine hydrochloride

5 The compound was prepared by coupling of 3,4-dichlorophenylacetic acid with 4-acetyl-
2-(R,S)-[(3'-(R)-hydroxy-1-pyrrolidine)methyl]piperazine. Then, this racemic mixture was
separated on a Chiralpak AD column using 100% acetonitrile as the eluant. Then, from the 2-(S),
3'-(R) enantiomer a HCl salt was generated (1.05 gm); mp: (HCl salt)130-135°C; $[\alpha]^{20} +28.8^\circ$
(0.75%; w/v MeOH). ^1H NMR (free base, 300 MHz, CDCl_3) δ 1.74 (1H, m), 2.13 (3H, s),
10 2.2(1H, m), 2.3-3.2 (10H, m), 3.45-3.71 (3H, m), 4.11 (1H, d) 4.21-4.74(2H, m), 4.55((1H, m),
7.10 (1H, $J= 8.25$ Hz, d), 7.41 (2H, $J= 8.28$ Hz, d); MS (FAB) 414 ($\text{M} + \text{H})^+$; Anal. Calcd. for
 $\text{C}_{19}\text{H}_{25}\text{Cl}_2\text{N}_3\text{O}_3\text{HCl}$: C, 50.62; H, 5.81; N, 9.32. Found: C, 50.19; H, 5.86; N, 9.06.

Ref.

15 Naylor, A.; Judd, D. B.; Lloyd, J. E.; Scopes, D. I. C.; Hayes, A. G.; Birch, P. J. *J. Med. Chem.* 1993, 36, 2075-2083 and references cited in there.
U.S. Patent 5,116,842; Naylor et al; 1992.

Compounds of formula II

20 **General procedure for DCC/pyr coupling.** With stirring at 25°C under N_2 , DCC (2.06 eq) and CH_2Cl_2 were added to a mixture of the acid (2 eq) and pyridine (2.06 eq) in CH_2Cl_2 . After 1-2 min, a solution of the amine (1 eq) in CH_2Cl_2 was added, and the mixture was stirred at 25°C under N_2 overnight. The final concentration of the mixture is around 0.1-0.3 mM with respect to the amine. Sat'd. NaHCO_3 (2 mL) was added to destroy excess active esters before the 25 mixture was filtered through celite, and the DCU was washed with CH_2Cl_2 . The filtrate was then partitioned between sat'd NaHCO_3 and CH_2Cl_2 , which was dried (Na_2SO_4), filtered through celite, and evaporated. Toluene was added to azeotrope off pyridine before the crude product was chromatographed and converted to the HCl salt.

Compounds having the following structures were prepared:



(±)-1, X = -OMe

(±)-2, X = -NO₂

(±)-3, X = -OMe, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

(±)-4, X = -OH, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

(±)-5, X = -OCH₂CO₂H, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

5 (±)-6, X = -OMe, R₁ = R₂ = phenyl

(±)-7, X = -OH, R₁ = R₂ = phenyl

(±)-8, X = -NO₂, R₁ = -H, R₂ = 2-NO₂-4,5-Cl₂-phenyl

(±)-9, X = -NO₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

(±)-10, X = -NH₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

10 (±)-11, X = -NO₂, R₁ = -H, R₂ = 4-methylsulfonylphenyl

(±)-12, X = -N(CH₂CO₂tBu)₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

(±)-13, X = -N(CH₂CO₂H)₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

(±)-14, X = -N(CH₂CO₂Et)₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

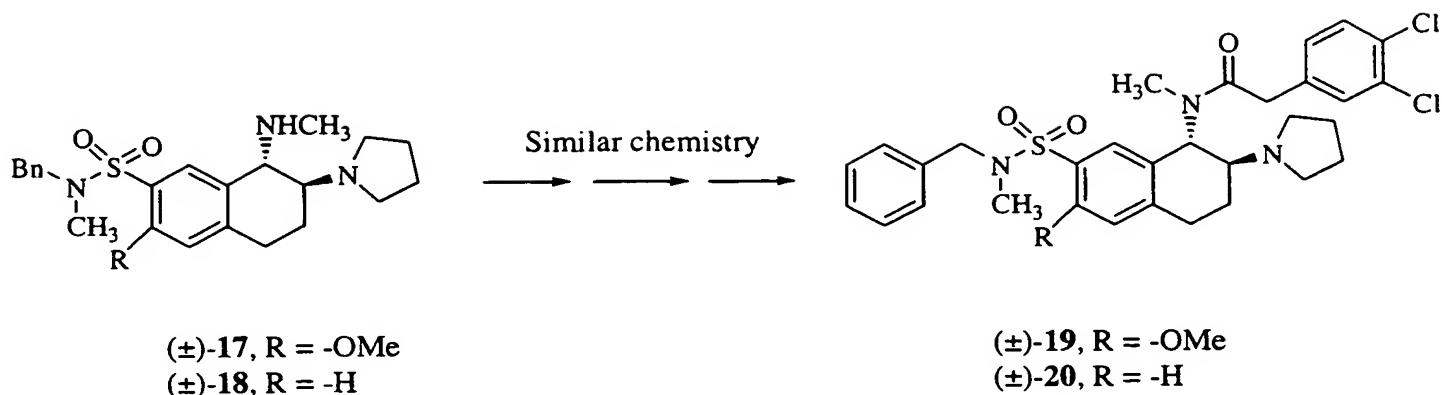
(±)-15, X = -NHPO₃Et₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

15 (±)-16, X = -N(CH₂)₂PO₃Et₂, R₁ = -H, R₂ = 3,4-Cl₂-phenyl

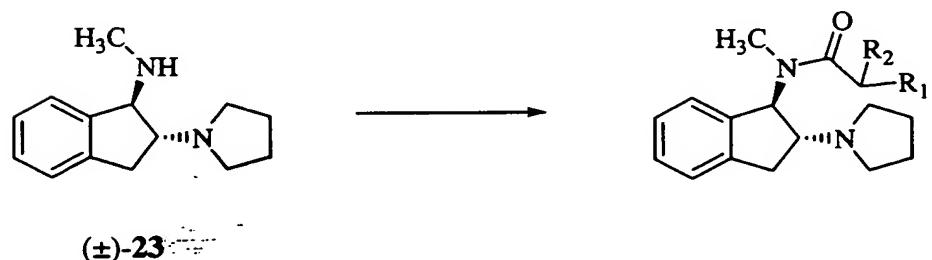
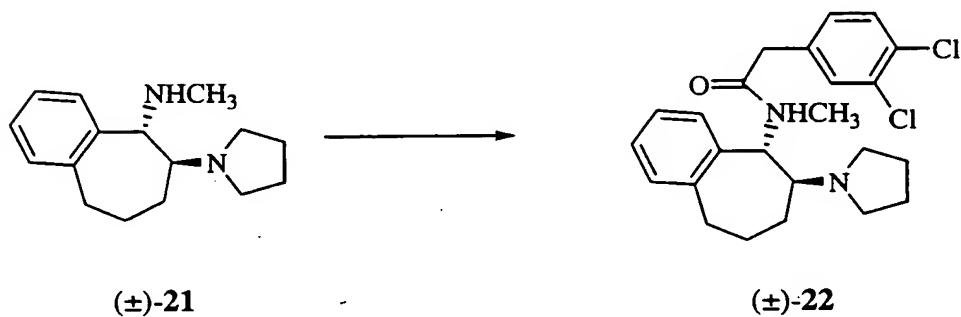
Intermediates (±)-1 and (±)-2 were prepared via reported methods from the appropriate starting materials.⁵ Compounds (±)-3 and (±)-4 are known compounds prepared via reported methods.⁵ Compounds (±)-5 through (±)-16 were prepared by DCC coupling of either (±)-1 or (±)-2 to an arylacetic acid followed by demethylation or reduction to allow peripheralization.

Ref.

(5) Rajagopalan, P. et al. Bioorg. Med. Chem. Letters 1992, 2, 721-726.



5 Intermediates **17** and **18** were prepared via known methods from 6-methoxy-1-tetralone and 1-tetralone, respectively. Intermediates **17** and **18** were coupled to 3,4-dichlorophenylacetic acid to produce $(\pm)\text{-19}$ and $(\pm)\text{-20}$.



10

15

Intermediates $(\pm)\text{-21}$ and $(\pm)\text{-23}$ were prepared via similar chemistry from 1-benzosuberone and (\pm) -trans-2-bromo-1-indanol.1 Compounds $(\pm)\text{-22}$, $(\pm)\text{-25}$ (Niravoline),⁶ and

(\pm)-27 are known compounds prepared via reported chemistry.¹ Compounds (\pm)-24 through (\pm)-29 were prepared by DCC coupling to the appropriate arylacetic acid.

Ref.

(6) Bellissant, E. et al. J. Pharmacol. Exp. Ther. 1996, 278, 232-242.

5

Representative examples of formula II follow.

Example 33

2-{7-[(\pm) -trans-1-(N-3,4-dichlorophenylacetamido-N-methylamino)-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphthoxy]}acetic acid ((\pm)-5)

With stirring at 25 °C under N₂, t-butyl bromoacetate (0.35 mL, 2.38 mmol) was added to a mixture of (\pm)-4 (0.688 g, 1.59 mmol) and K₂CO₃ (0.5 g, 3.6 mmol) in DMF (8 mL), and the mixture was stirred at 25 °C under N₂ overnight before the mixture was evaporated under high 15 vacuum. The residue was partitioned between sat'd NaHCO₃ and CH₂Cl₂ (2 X 100 mL), which was dried (Na₂SO₄), filtered through celite, and evaporated. The t-butyl ester intermediate was flash column chromatographed twice eluting with CH₂Cl₂:2% NH₃:2% MeOH and CH₂Cl₂:2% NH₃:1% MeOH, respectively. The t-butyl ester was then deprotected in a mixture of THF (4 mL) and conc. HCl (2 mL) with stirring at 25 °C overnight and at 50 °C for 1h before the mixture was 20 evaporated. The residue was then dissolved in a mixture of trifluoroacetic acid (2 mL), 4 N HCl (2 mL), and anisole (1 drop), and stirred at 25 °C for 2.5 days before the mixture was evaporated. The oily residue was triturated with Et₂O and sonicated to yield (\pm)-5·HCl (0.259 g, 31%): m.p. (HCl salt) 138 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.7-2.1 (br s, 4H, -CH₂CH₂-), 2.2-4.8 (complex, 13H, 6 -CH₂- and 1 -CH-), 2.79 (s, 3H, -NCH₃), 5.98 (d, J = 10.3 Hz, 1H, -CH-), 6.40 (s, 1H, aromatic), 6.82 (m, 1H, aromatic), 7.12 (d, J = 8.2 Hz, 1H, aromatic), 7.39 (d, J = 8.3 Hz, 1H, aromatic), 7.63 (m, 2H, aromatic). MS (FAB) m/z 491. Anal. (C, H, N) C₂₅H₂₈N₂O₄Cl₂·HCl.

Example 34

2,2-Diphenyl-N-methyl-N-[(\pm) -trans-2-(1-pyrrolidinyl)-7-methoxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((\pm)-6)

30

This compound was prepared via the general DCC/pyr coupling method from (\pm)-1 (1.453 g, 5.58 mmol), diphenylacetic acid (2.369 g, 11.16 mmol), DCC (2.373 g, 11.50 mmol), and pyridine (0.93 mL, 11.5 mmol). The product was flash column chromatographed eluting with

CH₂Cl₂:2% NH₃: 1% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from MeOH-Et₂O to yield (±)-6 HCl (1.7 g, 63%): m.p. (HCl salt) >250 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.8-2.0 (br s, 4H, -CH₂CH₂-), 2.2-3.9 (complex, 9H, 4 -CH₂- and 1 -CH-), 5 2.79 (s, 3H, -NCH₃), 3.48 (s, 3H, -OCH₃), 5.66 (s, 1H, -CH-), 6.1 (d, J = 9.4 Hz, 1H, -CH-), 6.23 (s, 1H, aromatic), 6.77 (d of d, J = 2.4 Hz and 8.4 Hz, 1H, aromatic), 7.09 (d, J = 8.5 Hz, 1H, aromatic), 7.2-7.5 (complex, 10H, aromatic). MS (FAB) m/z 455. Anal. (C, H, N) C₃₀H₃₄N₂O₂ HCl.

Example 35

10 2,2-Diphenyl-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-hydroxy-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((±)-7)

With stirring in dry ice-acetone under N₂, 1.0 M BBr₃ in CH₂Cl₂ (19.7 mL) was added at a fast drop rate to a solution of (±)-6 (1.491 g, 3.28 mmol) in CH₂Cl₂ (20 mL), and the mixture 15 was allowed to slowly warm to 25 °C under N₂ as the dry ice sublimed. After 6.5 h, the mixture was quenched with MeOH with ice-H₂O cooling and diluted with CH₂Cl₂ (50 mL). The mixture was partitioned between sat'd NaHCO₃ and CH₂Cl₂. Some yellowish precipitate was extracted into CH₂Cl₂ by adding some MeOH. The organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The product was flash colum chromatographed eluting with CHCl₃:2% 20 NH₃:2% MeOH to yield (±)-7 (0.426 g, 30%). Part of the free base was converted to the HCl salt with 1.0 M HCl in Et₂O: ¹H NMR (free base, CDCl₃) δ 1.5-1.8 (br s, 4H, -CH₂CH₂-), 1.8-2.9 (complex, 9H, 4 -CH₂- and 1 -CH-), 2.55 (s, 3H, -NCH₃), 5.21 (s, 1H, -CH-), 5.83 (d, J = 8.6 Hz, 1H, -CH-), 6.22 (s, 1H, aromatic), 6.46 (m, 1H, aromatic), 6.78 (d, J = 8.1 Hz, 1H, aromatic), 7-7.4 (complex, 10H, aromatic). MS (FAB) m/z 441. Anal. (C, H, N) C₂₉H₃₂N₂O₂ HCl·H₂O.

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Example 36

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((±)-8)

30 This compound was prepared via the general DCC/pyr coupling method from (±)-2 (0.5790 g, 2.103 mmol), 2-nitro-4,5-dichlorophenylacetic acid (1.0512 g, 4.204 mmol), DCC (0.8948 g, 4.34 mmol), and pyr (0.35 mL, 4.3 mmol). After stirring at 25 °C overnight, more 2-nitro-4,5-dichlorophenylacetic acid (1.0510 g, 4.203 mmol), DCC (0.8946 g, 4.34 mmol), and CH₂Cl₂ (10 mL) were added, and after 5 h, the reaction was worked up according to the general

procedure. The crude product was purified by gravity column eluting with CH_2Cl_2 :2% NH_3 before it was converted to the HCl salt with 1.0 M HCl in Et_2O and washed with hot MeOH to yield $(\pm)\text{-8HCl}$ (0.4948 g, 43% yield): m.p. (HCl salt) >250 $^{\circ}\text{C}$; ^1H NMR (HCl salt, DMSO-d_6) δ 1.8-2. (br s, 4H, $-\text{CH}_2\text{CH}_2-$), 2.2-4.6 (complex, 11H, 5 $-\text{CH}_2-$ and 1 $-\text{CH}-$), 2.9 (s, 3H, $-\text{NCH}_3$), 6.1 (d, $J = 10.2$ Hz, 1H, $-\text{CH}-$), 7.53 (d, $J = 8.5$ Hz, 1H, aromatic), 7.89 (s, 1H, aromatic), 7.91 (s, 1H, aromatic), 8.12 (d of d, $J = 2.2$ Hz and 8.5 Hz, 1H, aromatic), 8.4 (s, 1H, aromatic). MS (FAB) m/z 507. Anal. (C, H, N) $\text{C}_{23}\text{H}_{24}\text{N}_4\text{O}_5\text{Cl}_2\text{HCl}$.

10 **Example 37**

2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((±)-9)

This compound was prepared via the general DCC/pyr coupling procedure from $(\pm)\text{-2}$ (1.8173 g, 6.600 mmol), 3,4-dichlorophenylacetic acid (2.7066 g, 13.20 mmol), DCC (2.8057 g, 13.60 mmol), and pyr (1.10 mL, 13.6 mmol). The product was purified by flash column eluting with CH_2Cl_2 :2% NH_3 :1% MeOH before it was converted to the HCl salt with $\text{Et}_2\text{O-HCl}$ and washed with hot MeOH to yield $(\pm)\text{-9HCl}$ (2.49 g, 76%): m.p. (HCl salt) 255-257 $^{\circ}\text{C}$; ^1H NMR (HCl salt, DMSO-d_6) δ 1.8-2 (br s, 4H, $-\text{CH}_2\text{CH}_2-$), 2-4.2 (complex, 11H, 5 $-\text{CH}_2-$ and 1 $-\text{CH}-$), 2.83 (s, 3H, $-\text{NCH}_3$), 6.1 (d, $J = 9.8$ Hz, 1H, $-\text{CH}-$), 7.3-7.7 (complex, 5H, aromatic), 8.06 (d of d, $J = 2.4$ Hz and 8.6 Hz, 1H, aromatic). MS (FAB) m/z 462. Anal. (C, H, N) $\text{C}_{23}\text{H}_{25}\text{N}_3\text{O}_3\text{Cl}_2\text{HCl}$.

25 **Example 38**

2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-amino-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((±)-10)

With stirring at 55 $^{\circ}\text{C}$, Raney nickel (50% slurry in H_2O) was added in small portions to a mixture of $(\pm)\text{-9}$ (2.10 g, 4.54 mmol) and hydrazine hydrate (4 mL) in EtOH (60 mL) until all hydrazine was decomposed in 30 min. The mixture was filtered through celite, and the Raney nickel was washed with hot MeOH (120 mL). The filtrate was evaporated and dried in vacuo before the residue was partitioned between sat'd NaHCO_3 and CH_2Cl_2 , which was dried (Na_2SO_4), filtered through celite, and evaporated. The product was purified by gravity column eluting with CHCl_3 :2% NH_3 :0.5% MeOH before it was converted to the HCl salt with $\text{Et}_2\text{O-HCl}$ to yield $(\pm)\text{-10HCl}$ (0.3 g, 14%, unoptimized): m.p. (HCl salt) >250 $^{\circ}\text{C}$; ^1H NMR (free base, CDCl_3) δ 1.64 (br s, 4H, $-\text{CH}_2\text{CH}_2-$), 1.9-3.8 (complex, 11H, 5 $-\text{CH}_2-$ and 1 $-\text{CH}-$), 2.59 (s, 3H, -

NCH₃), 5.8 (d, J = 9.7 Hz, 1H, -CH-), 6.29 (s, 1H, aromatic), 6.43 (d, J = 8 Hz, 1H, aromatic), 6.8 (d, J = 8 Hz, 1H, aromatic), 7.17 (d, J = 8 Hz, 1H, aromatic), 7.3 (m, 2H, aromatic). MS (FAB) m/z 432. Anal. (C, H, N) C₂₃H₂₇N₃OCl₂·2HCl.

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Example 39**2-(4-Methylsulfonylphenyl)-N-methyl-N-[\pm]-trans-2-(1-pyrrolidinyl)-7-nitro-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((\pm)-11)**

10 This compound was prepared via the general DCC/pyr coupling procedure from (\pm)-2 (0.3414 g, 1.240 mmol), 4-methylsulfonylphenylacetic acid (0.5309 g, 2.478 mmol), DCC (0.5288 g, 2.563 mmol), and pyr (0.21 mL, 2.55 mmol). After stirring at 25 °C overnight, more of 4-methylsulfonylphenylacetic acid (0.5307 g, 2.477 mmol), DCC (1.1356 g, 5.504 mmol), and CH₂Cl₂ (13 mL) were added, and the mixture was worked up according to the general procedure 15 after another night of stirring. The product was purified by gravity column eluting with CHCl₃:2% NH₃:1% MeOH before it was converted to the HCl salt with Et₂O-HCl and washed with hot MeOH to yield (\pm)-11·HCl (0.4455 g, 76%): m.p. (HCl salt) 284-285 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.96 (br s, 4H, -CH₂CH₂-), 2.1-4.3 (complex, 11H, 5 -CH₂- and 1 -CH-), 2.88 (s, 3H, -NCH₃), 3.24 (s, 3H, -SO₂CH₃), 6.13 (d, J = 10 Hz, 1H, -CH-), 7.51 (d, J = 8.8 Hz, 1H, aromatic), 7.68 (m, 3H, aromatic), 7.9 (d, J = 8.7 Hz, 2H, aromatic), 8.08 (d of d, J = 2.6 Hz and 8.5 Hz, 1H, aromatic). MS (FAB) m/z 472. Anal. (C, H, N) C₂₄H₂₉N₃O₅S·HCl·0.25CH₂Cl₂.

25

Example 40**2-(3,4-Dichlorophenyl)-N-methyl-N-[\pm]-trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(t-butoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((\pm)-12)**

With stirring in ice-H₂O under N₂, t-butyl bromoacetate (0.34 mL, 2.32 mmol) was added dropwise to a mixture of (\pm)-10 (0.4014 g, 0.928 mmol) and NEt(iPr)₂ (0.81 mL, 4.64 mmol) in dry THF (10 mL). After 10 min, the mixture was stirred at 25 °C under N₂ overnight before more 30 t-butyl bromoacetate (0.30 mL) was added at 25 °C. After stirring overnight, more NEt(iPr)₂ (0.40 mL) and t-butyl bromoacetate (0.30 mL) were added, and after one more night of stirring, the mixture was partitioned between sat'd NaHCO₃ and CH₂Cl₂. The aqueous fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The crude product was purified by gravity column eluting with

CH₂Cl₂:2% NH₃:1% MeOH before part of the free base was converted to the HCl salt with 1.0 M HCl in Et₂O with stirring in ice-H₂O. The residue was sonicated in hexane to yield (\pm)-12·2HCl (0.1610 g, 25%, unoptimized): m.p. (HCl salt) 143 °C (dec); ¹H NMR (free base, CDCl₃) δ 1.39 (s, 9H, t-butyl), 1.43 (s, 9H, t-butyl), 1.65 (br s, 4H, -CH₂CH₂-), 1.9-4.1 (complex, 15H, 7 -CH₂- and 1 -CH-), 2.58 (s, 3H, -NCH₃), 5.8 (m, 1H, -CH-), 6.2-7.4 (complex, 6H, aromatic). MS (FAB) 660. Anal. (C, H, N) C₃₅H₄₇N₃O₅Cl₂·2HCl·0.5CH₃CN.

Example 41

2-(3,4-Dichlorophenyl)-N-methyl-N-{[\pm]-trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(carboxymethyl)amino]-1,2,3,4-tetrahydronaphth-1-yl}acetamide ((\pm)-13)

10 A solution of (\pm)-12 (0.35 g, 0.5 mmol) in 1:1 AcOH and 3 N HCl (8 mL) with some anisole (2 drops) was stirred at 25 °C overnight before conc. HCl (0.5 mL) was added, and the mixture was warmed to 40 °C for 1 h. Then some anisole (4 drops) was added, and the mixture 15 was stirred at 25 °C for 5 h before it was evaporated. The residue was sequentially evaporated from iPrOH and PhCH₃ before it was sonicated with Et₂O to yield (\pm)-13·HCl (0.2360 g, 81%): m.p. (HCl salt) 160 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.93 (br s, 4H, -CH₂CH₂-), 2.2-4.3 (complex, 15H, 7 -CH₂- and 1 -CH-), 2.79 (s, 3H, -NCH₃-), 5.93 (d, J = 10.7 Hz, 1H, -CH-), 6.37 (s, 1H, aromatic), 6.68 (d, J = 8.8 Hz, 1H, aromatic), 7.00 (d, J = 8.1 Hz, 1H, aromatic), 7.40 (d, J = 8.1 Hz, 1H, aromatic), 7.63 (m, 2H, aromatic). MS (FAB) m/z 490 (M+1-CH₂CO₂H). Anal. (C, H, N) C₂₇H₃₁N₃O₅Cl₂ 1HCl.

Example 42

2-(3,4-Dichlorophenyl)-N-methyl-N-{[\pm]-trans-2-[1-pyrrolidinyl]-7-[N,N-bis-(ethoxycarbonylmethyl)-amino]-1,2,3,4-tetrahydronaphth-1-yl}acetamide ((\pm)-14)

25 With stirring in ice-H₂O under N₂, ethyl bromoacetate (0.47 mL, 4.21 mmol) was added dropwise to a mixture of (\pm)-10 (0.3640 g, 0.842 mmol) and NEt(iPr)₂ (0.88 mL, 5.05 mmol) in dry THF (6 mL). After 10 min, the mixture was stirred at 25 °C under N₂ overnight before it was 30 partitioned between sat'd NaHCO₃ and CH₂Cl₂. The aqueous fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The product was purified by gravity column eluting with CH₂Cl₂:2% NH₃:1% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and washed with Et₂O to yield (\pm)-14·HCl (0.27 g, 47%): m.p. (HCl salt) 128 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.2 (m,

6H, 2 -CH₃), 1.9 (br s, 4H, -CH₂CH₂-), 2.2-4.4 (complex, 19H, 9 -CH₂- and 1 -CH-), 2.78 (s, 3H, -NCH₃), 5.9 (d, J = 10.3 Hz, 1H, -CH-), 6.14 (s, 1H, aromatic), 6.49 (d, J = 8.2 Hz, 1H, aromatic), 6.91 (d, J = 8.3 Hz, 1H, aromatic), 7.39 (d, J = 8.3 Hz, 1H, aromatic), 7.6 (m, 2H, aromatic). MS (FAB) m/z 605. Anal. (C, H, N) C₃₁H₃₉N₃O₅Cl₂·1.25HCl·0.3CH₃CN.

5

Example 43

2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-7-(N-diethylphosphoramido-amino)-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((±)-15)

10 With stirring in ice-H₂O under N₂, diethyl chlorophosphate (0.57 mL, 3.92 mmol) was added dropwise to a mixture of (±)-10 (0.3393 g, 0.785 mmol) and NEt(iPr)₂ (0.82 mL, 4.71 mmol) in dry THF (6 mL). After 10 min, the mixture was stirred at 25 °C under N₂ overnight before the mixture was evaporated and dried in vacuo. The residue was partitioned between sat'd NaHCO₃ and CH₂Cl₂. The aqueous fraction was extracted with more CH₂Cl₂, and the combined 15 organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The product was purified by gravity column eluting with CH₂Cl₂:2% NH₃:1.5% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and sonicated in Et₂O to yield (±)-15HCl (0.4205 g, 89%): m.p. (HCl salt) 247-249 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.2 (m, 6H, 2 -CH₃), 1.95 (br s, 4H, -CH₂CH₂-), 2.2-4.1 (complex, 15H, 7 -CH₂- and 1 -CH-), 2.75 (s, 3H, -NCH₃), 5.98 (d, J = 10.3 Hz, 1H, -CH-), 6.7 (s, 1H, aromatic), 6.9 (m, 1H, aromatic), 7.03 (d, J = 8.4 Hz, 1H, aromatic), 7.3 (d of d, J = 2 Hz and 8.2 Hz, 1H, aromatic), 7.6 (m, 2H, aromatic), 7.92 (d, J = 9.7 Hz, -NHP). MS (FAB) m/z 568. Anal. (C, H, N) C₂₇H₃₆N₃O₄PCl₂·HCl·0.25H₂O.

Example 44

2-(3,4-Dichlorophenyl)-N-methyl-N-[(±)-trans-2-[1-pyrrolidinyl]-7-[N-2-(diethylphosphoryl)ethyl-amino]-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((±)-16)

25 With stirring in ice-H₂O under N₂, diethyl 2-bromoethylphosphonate (0.8601 g, 3.52 mmol) was added to a mixture of (±)-10 (0.3042 g, 0.704 mmol) and NEt(iPr)₂ (0.74 mL, 4.2 mmol) in dry THF (4 mL). After 10 min, the mixture was stirred at 25 °C under N₂ for 2.5 days 30 before more diethyl 2-bromoethylphosphonate (0.8546 g) and NEt(iPr)₂ (0.74 mL, 4.2 mmol) were added. After stirring for 14 more days, the mixture was evaporated to dryness and dried in vacuo before the residue was partitioned between sat'd NaHCO₃ and CH₂Cl₂. The aqueous fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄),

filtered through celite, and evaporated. The product was purified by gravity column eluting with CH₂Cl₂:2% NH₃:1% MeOH and then by radial chromatography eluting with CH₂Cl₂:2% NH₃. The product was converted to the HCl salt with 1.0 M HCl in Et₂O and solidified by evaporation from CH₂Cl₂ and sonication with Et₂O to yield (\pm)-16HCl (0.2466 g, 52%): m.p. (HCl salt) 151 5 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.24 (t, J = 7 Hz, 6H, 2 -CH₃), 1.93 (br s, 4H, -CH₂CH₂-), 2-4.3 (complex, 19H, 9 -CH₂- and 1 -CH-), 2.8 (s, 3H, -NCH₃), 5.96 (d, J = 10.2 Hz, 1H, -CH-), 6.69 (br s, 1H, aromatic), 6.87 (d, J = 7.5 Hz, 1H, aromatic), 7.11 (d, J = 8.1 Hz, 1H, aromatic), 7.43 (d, J = 8.3 Hz, 1H, aromatic), 7.64 (m, 2H, aromatic). MS (FAB) m/z 596. Anal. (C, H, N) C₂₉H₄₀N₃O₄PCl₂·2HCl.

10

Example 45

2-(3,4-Dichlorophenyl)-N-methyl-N-[(\pm)-trans-2-(1-pyrrolidinyl)-6-methoxy-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((\pm)-19)

15 This compound was prepared via the general DCC/pyr coupling procedure from (\pm)-17 (0.6213 g, 1.40 mmol), 3,4-dichlorophenylacetic acid (0.5764 g, 2.81 mmol), DCC (0.5951 g, 2.88 mmol), and pyr (0.23 mL, 2.88 mmol). The product was gravity column chromatographed eluting with CH₂Cl₂:2% NH₃:1% MeOH and further purified by radial chromatography eluting with CH₂Cl₂:2% NH₃. The product was converted to the HCl salt with 1.0 M HCl in Et₂O to 20 yield (\pm)-19HCl (0.3 g, 32%): m.p. (HCl salt) 150 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.91 (br s, 4H, -CH₂CH₂-), 2.2-4.1 (complex, 11H, 5 -CH₂- and 1 -CH-), 2.55 (s, 3H, -NCH₃), 2.77 (s, 3H, -NCH₃), 3.88 (s, 3H, -OCH₃), 4.2 (s, 2H, -CH₂Ph), 6.0 (d, J = 9.7 Hz, 1H, -CH-), 7.10 (s, 1H, aromatic), 7.2-7.4 (complex, 7H, aromatic), 7.55 (m, 2H, aromatic). MS (FAB) m/z 630. Anal. (C, H, N) C₃₂H₃₇N₃O₄Cl₂S·HCl·0.5H₂O.

25

Example 46

2-(3,4-Dichlorophenyl)-N-methyl-N-[(\pm)-trans-2-(1-pyrrolidinyl)-7-(N-benzyl-N-methylaminosulfonyl)-1,2,3,4-tetrahydronaphth-1-yl]acetamide ((\pm)-20)

30 This compound was prepared via the general DCC/pyr coupling procedure from (\pm)-18 (0.4530 g, 1.095 mmol), 3,4-dichlorophenylacetic acid (0.4485 g, 2.19 mmol), DCC (0.4677 g, 2.27 mmol), and pyr (0.18 mL, 2.26 mmol). The product was purified by flash column eluting with CH₂Cl₂:2% NH₃ and then by radial chromatography eluting with CH₂Cl₂:2% NH₃. The product was converted to the HCl salt with 1.0 M HCl in Et₂O and then washed with hot MeOH

to yield (\pm)-20·HCl (0.33 g, 47%): m.p. (HCl salt) 251-254 °C; ^1H NMR (HCl salt, DMSO-d₆) δ 1.97 (br s, 4H, -CH₂CH₂-), 2.3-4.2 (complex, 13H, 6 -CH₂- and 1 -CH-), 2.49 (s, 3H, -NCH₃), 2.90 (s, 3H, -NCH₃), 6.17 (d, J = 10.4 Hz, 1H, -CH-), 7.2-7.8 (complex, 11H, aromatic). MS (FAB) m/z 600. Anal. (C, H, N) C₃₁H₃₅N₃SO₃Cl₂·HCl.

5

Example 47

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide ((\pm)-24)

10 This compound was prepared via the general DCC/pyr coupling procedure from (\pm)-23 (0.4265 g, 1.971 mmol), 2-nitro-4,5-dichlorophenylacetic acid (0.9859 g, 3.943 mmol), DCC (0.8350 g, 4.047 mmol), and pyr (0.33 mL, 4.06 mmol). The crude product was purified by silica gel column eluting with CH₂Cl₂:2% NH₃ before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from MeOH to yield (\pm)-24·HCl (0.3630 g, 38%, first crop): m.p. (HCl salt) 284-287 °C; ^1H NMR (HCl salt, DMSO-d₆) δ 1.8-2.1 (br s, 4H, -CH₂CH₂-), 2.84 (s, 3H, -NCH₃), 3- 4.4 (complex, 9H, 4 -CH₂- and 1 -CH-), 6.37 (d, J = 8 Hz, 1H, -CH-), 7.08 (br s, 1H, aromatic), 7.3 (m, 3H, aromatic), 7.92 (s, 1H, aromatic), 8.41 (s, 1H, aromatic). MS (FAB) m/z 448. Anal. (C, H, N) C₂₂H₂₃N₃O₃Cl₂·HCl.

20

Example 48

2-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[\pm -trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide ((\pm)-26)

25 This compound was prepared via the general DCC/pyr coupling procedure from (\pm)-23 (0.3229 g, 1.492 mmol), 2-nitro-4-trifluoromethylphenylacetic acid (0.5579 g, 2.24 mmol), DCC (0.5512 g, 2.67 mmol), and pyr (0.19 mL, 2.31 mmol). The crude product was gravity column chromatographed eluting with CH₂Cl₂:2% NH₃ before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from MeOH-Et₂O to yield (\pm)-26·HCl (0.3643 g, 50%): m.p. (HCl salt) 249-250 °C; ^1H NMR (HCl salt, DMSO-d₆) δ 1.8-2.1 (br s, 4H, -CH₂CH₂-), 2.89 (s, 3H, -NCH₃), 3-4.6 (complex, 9H, 4 -CH₂- and 1 -CH-), 6.40 (d, J = 8.1 Hz, 1H, -CH-), 7.1 (br s, 1H, aromatic), 7.3 (m, 3H, aromatic), 7.83 (d, J = 8.1 Hz, 1H, aromatic), 8.17 (d, J = 7.8 Hz, 1H, aromatic), 8.41 (s, 1H, aromatic). MS (FAB) m/z 448. Anal. (C, H, N) C₂₃H₂₄N₃O₃F₃·HCl.

Example 49**2,2-Diphenyl-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide ((±)-28)**

This compound was prepared via the general DCC/pyr coupling procedure from (±)-23
5 (0.2615 g, 1.209 mmol), diphenylacetic acid (0.5123 g, 2.41 mmol), DCC (0.5138 g, 2.49 mmol),
and pyr (0.20 mL, 2.5 mmol). The crude product was purified by gravity column eluting with
CH₂Cl₂:2% NH₃ before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized
from MeOH to yield (±)-28HCl (0.3815 g, 71%): m.p. (HCl salt) >300 °C; ¹H NMR (HCl salt,
10 DMSO-d₆; the cis-trans rotamers are observed in about 3.6 to 1 ratio. Only peaks for the major
rotamer are reported.) δ1.88 (br s, 4H, -CH₂CH₂-), 2.75 (s, 3H, -NCH₃), 3-4.2 (complex, 7H, 3 -
CH₂- and 1 -CH-), 5.61 (s, 1H, -CH-), 6.5 (d, J = 8 Hz, 1H, -CH-), 6.88 (d, J = 6.5 Hz, 1H,
aromatic), 7.1-7.4 (complex, 13 H, aromatic). MS (FAB) m/z 411. Anal. (C, H, N)
C₂₈H₃₀N₂O·HCl·0.75 H₂O.

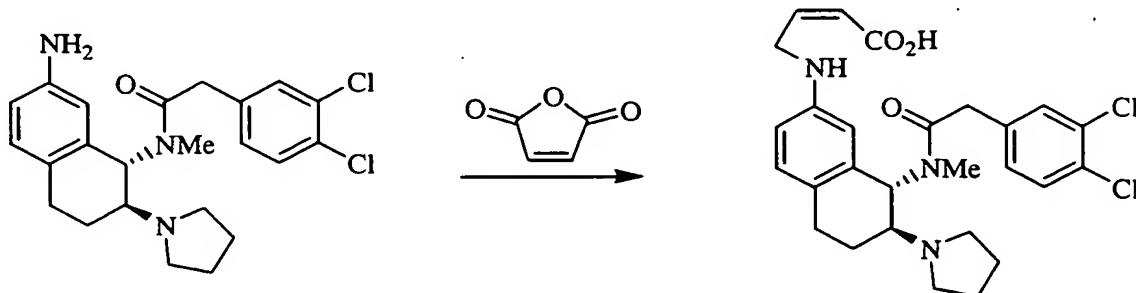
15

Example 50**2-(4-Methylsulfonylphenyl)-N-methyl-N-[(±)-trans-2-(1-pyrrolidinyl)-indan-1-yl]acetamide
((±)-29)**

This compound was prepared via the general DCC/pyr coupling procedure from (±)-23
20 (0.3271 g, 1.51 mmol), 4-methylsulfonylphenylacetic acid (0.6464 g, 3.017 mmol), DCC (0.6438,
3.12 mmol), and pyr (0.25 mL, 3.1 mmol). The product was purified by gravity column eluting
with CH₂Cl₂:2% NH₃ before it was converted to the HCl salt with 1.0 M HCl in Et₂O and
crystallized from MeOH-Et₂O to yield (±)-29HCl (0.5295 g, 78%): m.p. (HCl salt) 246-248 °C;
¹H NMR (HCl salt, DMSO-d₆) δ 1.8-2 (br s, 4H, -CH₂Cl₂-), 2.81 (s, 3H, -NCH₃), 2.9-4.2
25 (complex, 9H, 4-CH₂- and 1 -CH-), 3.21 (s, 3H, -SO₂CH₃), 6.4 (d, J = 8.1 Hz, 1H, aromatic), 7
(m, 1H, aromatic), 7.3 (m, 3H, aromatic), 7.58 (d, J = 8.1 Hz, 2H, aromatic), 7.9 (d, J = 7.8 Hz,
2H, aromatic). MS (FAB) m/z 413. Anal. (C, H, N) C₂₃H₂₈N₂SO₃·HCl·0.25H₂O.

The preparation of a compound of Formula II A is shown in Example 2a.

30

Example 2a(Z)-(\pm)-trans-[(7-Amino-2-(3,4-dichlorophenyl)-N-methyl-2-(1-pyrrolidinyl)-1,2,3,4-tetrahydronaphth-1-yl)acetamido]4-oxo-butenoic acid

5

1

To a solution of 7-amino compound (1)¹ (0.266 g, 0.614 mmol) in anhydrous THF (4.5 mL) under a nitrogen atmosphere was added a solution of maleic anhydride (0.0602 g, 0.614 mmol) in anhydrous THF (0.53 mL). The reaction mixture was stirred at room temperature for 20 h and the resulting solid was filtered, washed with THF and ether, and dried in vacuo. The solid was then suspended in hot water, filtered, and dried to give 2, 0.267 g (82%); mp 221-223°C; MS (FAB) 530 (M+1); ¹H NMR (200 MHz, DMSO-d₆) δ 1.50-1.93 (m, 2H), 2.00-3.10 (m, 9H), 2.66 (s, 3H), 3.83 (m, 2H), 5.80 (m, 1H), 6.22 (m, 2H), 7.10 (d, J=7.5 Hz, 1H), 7.26 (s, 1H), 7.35 (d, J=8.0 Hz, 1H), 7.48 (d, J=8.5 Hz, 1H), 7.55-7.65 (m, 2H). Anal. (C, H, N) C₂₇H₂₉N₃O₄Cl₂·0.5H₂O.

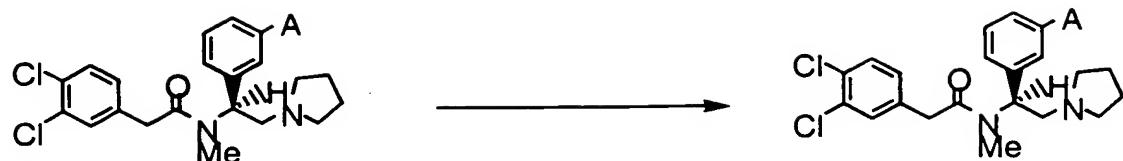
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Ref.

1. U.S. Patent 5,744,458

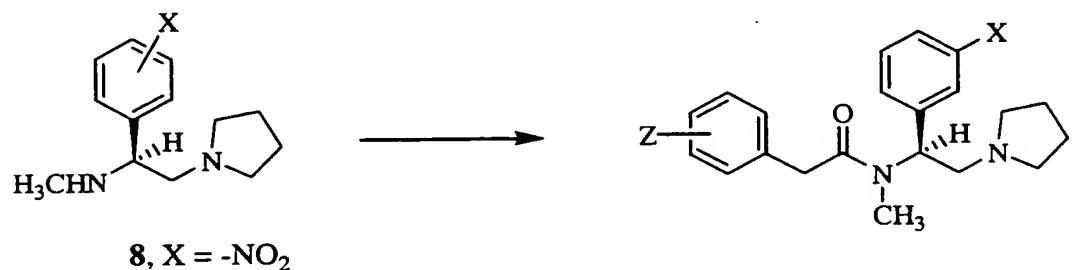
Compounds of formula III

Compounds having the following structures were prepared.

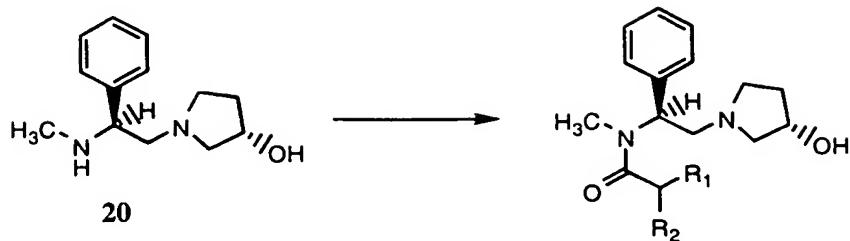


- 1 , A=-NH₂
- 2 , A=(R)-NHC(O)CH₂CH₂CH(NH₂)(CO₂H)
- 3 , A=(S)-NHC(O)CH₂CH(NH₂)(CO₂H)
- 4 , A=(R)-NHC(O)CH(NH₂)(CH₂CO₂H)
- 5 , A=(S)-NHC(O)CH(NH₂)(CH₂CO₂H)
- 6 , A=(S,S)-NHC(O)CH(CH₂CO₂H)NHC(O)CH(CH₂CO₂H)(NH₂)
- 7 , A=-N(SO₂Me)₂

Compounds 1-5 were prepared by the method described in Chang, A.-C.. Ph.D. Thesis, University of Minnesota-Twin Cities, 1995.



Compounds **9-19** were prepared from the appropriate arylacetic acids via DCC/pyr coupling, followed by reduction, deprotection, and/or derivatization via known chemistry. 20 Intermediate **8** was prepared via the method described in Chang, A.-C.. Ph.D. Thesis, University of Minnesota-Twin Cities, 1995.



Intermediate 20 was prepared via minor modifications of known methods.^{7,8} Compounds 23 (EMD60400) and 24 (EMD61753) are known compounds that were synthesized in-house via minor modifications of reported methods.⁹ Compounds 21, 22 and 25-27 were prepared by DCC coupling, following by reduction where applicable.

Ref.

(7) Costello, G. F. et al. *J. Med. Chem.* 1991, 34, 181-189.
 (8) Naylor, A. et al. *J. Med. Chem.* 1994, 37, 2138-2144.
 (9) Gottschlich, R. et al. *Bioorg. Med. Chem. Letters* 1994, 4, 677-682.

Example 51

2-(3,4-Dichlorophenyl)-N-methyl-N-[(1*S*)-1-[N-(S-aspartic acid-a-amide-S-aspartic acid-a-amido)-3-aminophenyl]-2-[1-pyrrolidinyl]ethyl]acetamide (6)

With stirring in ice-H₂O under N₂, 1,3-dicyclohexylcarbodiimide (DCC, 0.353 g, 1.711 mmol) and dry CH₂Cl₂ (2 mL) were added to a mixture of 5-t-butyl ester (0.311 g, 0.538 mmol), N-Boc-L-aspartic acid-b-t-butyl ester (0.495 g, 1.711 mmol), and 1-hydroxybenzotriazole (HOBT, 0.232 g, 1.717 mmol) in dry CH₂Cl₂ (8 mL). After 5 min, the mixture was stirred at 25 °C under N₂ overnight before H₂O (1 mL) was added, and the mixture was filtered through celite. The 1,3-dicyclohexylurea (DCU) was washed with CH₂Cl₂ (18 mL). The filtrate was partitioned between sat'd NaHCO₃ and CH₂Cl₂, which was dried (Na₂SO₄), filtered through celite, and evaporated. After flash column chromatography eluting with CH₂Cl₂:2% NH₃:2% MeOH, the protected intermediate (0.411 g, 90%) was dissolved in 3N HCl (4 mL), AcOH (4 mL) with

anisole (2 drops), and stirred at 25 °C overnight. The mixture was then evaporated to dryness, and evaporation from iPrOH then yielded ADL-01-0010-7: ^1H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.9 (s, 3H, -NCH₃), 6.1 (br m, 1H, -CH-). MS (FAB) m/z 636. Anal. (C, H, N) C₂₉H₃₅N₅O₇Cl₂ 1.5 HCl 0.25iPrOH.

5

Example 52

2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[N-(bis-methylsulfonamido)-3-aminophenyl]-2-[1-pyrrolidinyl]ethyl]acetamide (7)

10 With stirring at 25 °C, a solution of methanesulfonyl chloride (MsCl, 0.25 mL, 3.2 mmol) in dry CH₂Cl₂ (0.75 mL) was added to a mixture of ADL-01-0007-3 (0.225 g, 0.554 mmol) and Et₃N (1 mL, 7 mmol) in dry CH₂Cl₂ (4 mL), and the mixture was stirred at 25 °C fitted with a drying tube. After 5 h, more CH₂Cl₂ (6 mL), MsCl (0.5 mL), and Et₃N (2 mL) were added, and the mixture was stirred at 25 °C overnight before it was partitioned between CH₂Cl₂ (50 mL) and sat'd NaHCO₃. The aqueous fraction was extracted with more CH₂Cl₂ (25 mL), and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. Acetonitrile was used to azeotrope off Et₃N before the product was gravity column chromatographed twice eluting with CH₂Cl₂:2% NH₃:2% MeOH. The pure product was then treated with 1.0 M HCl in Et₂O to yield 7HCl (0.131 g, 39%, unoptimized): m.p. (HCl salt) 145 °C (dec); ^1H NMR (free base, CDCl₃) δ 1.7 (br s, 4H, -CH₂CH₂-), 2.4-3.8 (complex, 8H, 4 -CH₂-), 2.7 (s, 3H, -NCH₃), 3.37 (s, 6H, 2 -SO₂CH₃), 6.1 (m, 1H, -CH-), 7.1-7.4 (complex, 7H, aromatic). MS (FAB) m/z 562. Anal. (C, H, N) C₂₃H₂₉N₃O₅S₂Cl₂ HCl 0.75H₂O.

Example 53

2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (10)

25 This compound was prepared via the general DCC/pyr coupling procedure from **8** (1.4886 g, 5.97 mmol), 2-nitrophenylacetic acid (2.1619 g, 11.93 mmol), DCC (2.5402 g, 12.31 mmol), and pyridine (1.00 mL, 12.36 mmol). The crude product was converted to the HCl salt with Et₂O-HCl without chromatography and crystallized from MeOH-Et₂O. The first crop was recrystallized again from MeOH-Et₂O to yield **10**HCl (1.3663 g, 51%): m.p. (HCl salt) 258-259 °C; ^1H NMR (HCl salt, DMSO-d₆) δ 1.97 (br s, 4H, -CH₂CH₂-), 2.91 (s, 3H, -NCH₃), 3.11-4.45 (complex, 8H,

4 -CH₂), 6.17 (m, 1H, -CH-), 7.51-8.25 (complex, 8H, aromatic). MS (FAB) m/z 413. Anal. (C, H, N) C₂₁H₂₄N₄O₅·HCl·0.25H₂O.

Example 54

5 **2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (9)**

With stirring at 55 °C, Raney nickel was added in small quantities to a mixture of 10 (0.9857 g, 2.3899 mmol) and hydrazine hydrate (55%, 2 mL) in EtOH (30 mL) until gas 10 evolution stopped in about 10 min. The mixture was then filtered through celite, and the Raney nickel was washed with hot MeOH (100 mL). The filtrate was evaporated and dried in vacuo before the residue was partitioned between sat'd NaHCO₃ and CH₂Cl₂, which was dried (Na₂SO₄), filtered through celite, and evaporated. The product was gravity column chromatographed eluting with CHCl₃:2% NH₃:2% MeOH before it was converted to the HCl salt 15 with Et₂O-HCl to yield 9·3HCl (0.3159 g, 29%, unoptimized): m.p. (HCl salt) 219-222 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.98 (br s, 4H, -CH₂CH₂-), 2.87 (s, 3H, -NCH₃), 3.2-4.3 (complex, 8H, 4 -CH₂), 6.1 (m, 1H, -CH-), 7.11-7.45 (complex, 8H, aromatic). MS (FAB) m/z 353. Anal. (C, H, N) C₂₁H₂₈N₄O·3HCl·0.25H₂O.

20 **Example 55**

2-(N-Diethyl phosphoramidate-2-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (11)

With stirring in ice-H₂O under N₂, diethyl chlorophosphate (0.53 mL, 3.67 mmol) was 25 added to a mixture of 9 (0.2394 g, 0.6792 mmol) and NEt(iPr)₂ (0.77 mL, 4.40 mmol) in dry THF (5 mL). After 10 min, the mixture was stirred at 25 °C under N₂ for 3.5 days before it was diluted with CH₂Cl₂, evaporated, and dried in vacuo. The residue was partitioned between sat'd NaHCO₃ and CH₂Cl₂. The aqueous fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The product was 30 chromatographed eluting with CH₂Cl₂: 2% NH₃: 2% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from iPrOH-Et₂O to yield 11·HCl (0.2364 g, 53%): m.p. (HCl salt) 184-186 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.2 (m, 12H, 4 -CH₃), 1.96 (br s, 4H, -CH₂CH₂-), 2.81 (s, 3H, -NCH₃), 3-4 (complex, 16H, 8 -CH₂), 6.05 (m, 1H, -CH-), 6.7-7.3

(complex, 9H, aromatic and 1 NH), 8.08 (d, J = 9.4 Hz, 1H, NHP). MS (FAB) m/z 625. Anal. (C, H, N) $C_{29}H_{46}N_4O_7P_2$ HCl.

Example 56

2-(N-Bis-sulfonamido-2-aminophenyl)-N-methyl-N-[(1*S*)-1-(N-bis-sulfonamido-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (12)

With stirring at 0 °C under N₂, MsCl (0.61 mL, 7.87 mmol) was added to a mixture of **9** (0.2774 g, 0.787 mmol) and Et₃N (2.2 mL, 15.7 mmol) in CH₂Cl₂ (8 mL). After 10-15 min, the mixture was stirred at 25 °C under N₂ overnight before the mixture was partitioned between sat'd NaHCO₃ and CH₂Cl₂. The aqueous fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. Acetonitrile was added to azeotrope off Et₃N. The product was flash-column chromatographed eluting with CH₂Cl₂: 2% NH₃ before it was converted to the HCl salt with 1.0 M HCl in Et₂O to yield **12·HCl** (0.3564 g, 65%): m.p. (HCl salt) 180 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.76 (s, 3H, -NCH₃), 3-4.3 (complex, 8H, 4 -CH₂-), 3.53 (s, 12 H, 4 -SO₂CH₃), 6.25 (m, 1H, -CH-), 7.3-7.6 (complex, 8H, aromatic). MS (FAB) m/z 665. Anal. (C, H, N) C₂₅H₃₆N₄O₉S₄·HCl·MeOH.

Example 57

2-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[*(1S*)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (13)

This compound was prepared via the general DCC/pyr coupling procedure from **8** (0.3690 g, 1.4801 mmol), 2-nitro-4,5-dichlorophenylacetic acid (0.7301 g, 2.920 mmol), DCC (0.6213 g, 3.01 mmol), and pyridine (0.24 mL, 3.01 mmol). The crude product was converted to the HCl salt with Et₂O-HCl without chromatography and crystallized from MeOH to yield **13**·HCl (0.3232 g, 42%): m.p. (HCl salt) 165 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.93 (s, 3H, -NCH₃), 3.1-4.3 (complex, 6H, 3 -CH₂-), 4.4 (s, 2H, benzylic methylene), 6.2 (m, 1H, -CH-), 7.7-7.8 (m, 2H, aromatic), 7.9 (s, 1H, aromatic), 8.14 (s, 1H, aromatic), 8.27 (d, J = 7.7 Hz, 1H, aromatic), 8.43 (s, 1H, aromatic). MS (FAB) m/z 481. Anal. (C, H, N) C₂₁H₂₂N₄O₅Cl₂·HCl·0.5MeOH.

Example 58**2-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (14)**

5 This compound was prepared via the general DCC/pyr coupling procedure from **8** (0.5138 g, 2.061 mmol), 4-methylsulfonylphenylacetic acid (0.8825 g, 4.119 mmol), DCC (0.8771 g, 4.251 mmol), and pyridine (0.34 mL, 4.245 mmol). The crude product was gravity column chromatographed eluting with CHCl_3 :2% NH_3 before it was converted to the HCl salt with 1.0 M HCl in Et_2O and crystallized from MeOH to yield **14**:HCl (0.4695 g, 47%): m.p. (HCl salt) 276-277 °C; ^1H NMR (HCl salt, DMSO-d_6) δ 2.0 (br s, 4H, $-\text{CH}_2\text{CH}_2-$), 2.92 (s, 3H, $-\text{NCH}_3$), 3.2 (s, 3H, $-\text{SO}_2\text{CH}_3$), 3.2-4.3 (complex, 8H, 4 $-\text{CH}_2-$), 6.25 (m, 1H, $-\text{CH}-$), 7.61 (d, $J = 7.2$ Hz, 2H, aromatic), 7.75 (m, 2H, aromatic), 7.89 (d, $J = 7$ Hz, 2H, aromatic), 8.12 (s, 1H, aromatic), 8.25 (m, 1H, aromatic). MS (FAB) m/z 446. Anal. (C, H, N) $\text{C}_{22}\text{H}_{27}\text{N}_3\text{O}_5\text{S}\cdot\text{HCl}$.

10

Example 59**2-(N-Butyloxycarbonyl-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (18)**

15 This compound was prepared via the general DCC/pyr coupling method from **8** (1.9948 g, 8.001 mmol), N-Boc-4-aminophenylacetic acid (3.0589 g, 12.173 mmol), DCC (2.6602 g, 12.89 mmol), and pyridine (1.04 mL, 12.9 mmol). The crude product was gravity column chromatographed eluting with CH_2Cl_2 : 2% NH_3 : 1% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et_2O and crystallized from MeOH to yield **18**:HCl (0.4891 g, 12%, first crop): m.p. (HCl salt) 170 °C (dec); ^1H NMR (HCl salt, DMSO-d_6) δ 1.49 (s, 9H, t-butyl), 2.01 (br s, 4H, $-\text{CH}_2\text{CH}_2-$), 2.83 (s, 3H, $-\text{NCH}_3$), 3.1-4.15 (complex, 8H, 4 $-\text{CH}_2-$), 6.27 (m, 1H, $-\text{CH}-$), 7.17 (d, $J = 8$ Hz, 2H, aromatic), 7.39 (d, $J = 8$ Hz, 2H, aromatic), 7.7 (m, 2H, aromatic), 8.09 (s, 1H, aromatic), 8.23 (d, $J = 6$ Hz, 1H, aromatic), 9.3 (s, 1H, $-\text{NH}_2$). MS (FAB) 483. Anal. (C, H, N) $\text{C}_{26}\text{H}_{34}\text{N}_4\text{O}_5\cdot\text{HCl}\cdot 0.25\text{ H}_2\text{O}$.

20

25

Example 602-(4-Aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (15)

5 The product from Example 59 (2.9211 g, 6.053 mmol) and anisole (2 drops) were mixed in AcOH (10 mL) and 4N HCl (10 mL) and stirred at 25 °C overnight, fitted with a drying tube. The mixture was adjusted to pH 13 with 1N NaOH with stirring in ice-H₂O and then extracted with CH₂Cl₂ (2 X 70 mL). The combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The product was gravity column chromatographed eluting with CHCl₃:2% 10 NH₃ before it was converted to the HCl salt with Et₂O-HCl to yield **15**·HCl (0.5531 g, 22%, unoptimized): m.p. (HCl salt) 200 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.98 (br s, 4H, -CH₂CH₂-), 2.86 (s, 3H, -NCH₃), 3.2-4.3 (complex, 8H, 4 -CH₂-), 6.25 (m, 1H, -CH-), 7.16 (d, J = 7.4 Hz, 2 H, aromatic), 7.33 (d, J = 7.5 Hz, 2H, aromatic), 7.7 (m, 2H, aromatic), 8.08 (s, 1H, aromatic), 8.23 (m, 1H, aromatic). MS (FAB) m/z 383. Anal. (C, H, N)

15 C₂₁H₂₆N₄O₃·2HCl·0.75H₂O.

Example 612-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (16)

20 With stirring in ice-H₂O under N₂, a solution of MsCl (1.56 mL, 20.17 mmol) in CH₂Cl₂ (6 mL) was added dropwise over 2-3 min to a mixture of **15** (1.5430 g, 4.0344 mmol) and Et₃N (5.6 mL, 40 mmol) in CH₂Cl₂ (24 mL). After 10 min, the mixture was stirred at 25 °C under N₂ overnight before the mixture was partitioned between CH₂Cl₂ and sat'd NaHCO₃. The aqueous 25 fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. Acetonitrile was added to azeotrope off Et₃N before the crude product was flash column chromatographed eluting with CH₂Cl₂:2% NH₃. The product was converted to the HCl salt with 1.0 M HCl in Et₂O and washed with hot MeOH to yield **16**·HCl (1.3091 g, 56%, first crop): m.p. (HCl salt) 257-259 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.99 (br s, 4H, -CH₂CH₂-), 2.87 (s, 3H, -NCH₃), 3.15-4.3 (complex, 8H, 4 -CH₂-), 3.51 (s, 6H, 2 -SO₂CH₃), 6.25 (m, 1H, -CH-), 7.4 (m, 4H, aromatic), 7.7 (m, 2H, aromatic), 8.1 (s, 1H, aromatic), 8.21 (m, 1H, aromatic). MS (FAB) m/z 539. Anal. (C, H, N)

30 C₂₃H₃₀N₄O₇S₂·HCl·0.5CH₂Cl₂.

Example 622-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (17)

5 This compound was prepared from **16** (1.0729 g, 1.992 mmol), Raney nickel, and hydrazine hydrate (2 mL) in EtOH (30 mL). The conditions were similar to those used for the preparation of **9**. The product was gravity column chromatographed eluting with CH₂Cl₂:2% NH₃, and the pure fractions were converted to the HCl salt with 1.0 M HCl in Et₂O to yield 17HCl (0.1194 g, 11%, unoptimized): m.p. (HCl salt) 252-255 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.86 (s, 3H, -NCH₃), 3.1-4.2 (complex, 8H, 4 -CH₂-), 3.54 (s, 6H, 2 -SO₂CH₃), 6.1 (m, 1H, -CH-), 6.8-7.5 (complex, 8H, aromatic). MS (FAB) m/z 509. Anal. (C, H, N) C₂₃H₃₂N₄O₅S₂ 1.75HCl.

10

Example 632-(N-Bis-sulfonamido-4-aminophenyl)-N-methyl-N-[(1S)-1-(N-diethyl phosphoramidate-3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide (19)

15 With stirring in ice-H₂O under N₂, diethyl chlorophosphate (0.84 mL, 5.81 mmol) was added to a mixture of **17** (0.7383 g, 1.4514 mmol) and NEt(iPr)₂ (1.5 mL, 8.7 mmol) in dry THF (15 mL). After 10 min, the mixture was stirred at 25 °C under N₂ overnight before more THF (15 mL), NEt(iPr)₂ (0.76 mL), and diethyl chlorophosphate (0.42 mL) were sequentially added. After 3 h, the mixture was quenched with H₂O, diluted with CH₂Cl₂, evaporated, and dried in vacuo. The residue was partitioned between CH₂Cl₂ and sat'd NaHCO₃. The aqueous fraction was extracted with more CH₂Cl₂, and the combined organic fraction was dried (Na₂SO₄), filtered through celite, and evaporated. The crude product was flash column chromatographed eluting with CH₂Cl₂:2% NH₃:1.5% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from MeOH to yield 19HCl (0.3274 g, 33%): m.p. (HCl salt) 245-247 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.193 (t, J = 7 Hz, 6H, 2 -CH₃), 1.95 (br s, 4H, -CH₂CH₂-), 2.81 (s, 3H, -NCH₃), 3.1-4.1 (complex, 12H, 6 -CH₂-), 3.52 (s, 6H, 2 -SO₂CH₃), 6.1 (m, 1H, -CH-), 25 6.79 (d, J = 7.3 Hz, 1H, aromatic), 6.91 (s, 1H, aromatic), 6.99 (d, J = 7.7 Hz, 1H, aromatic), 7.23 (t, J = 7.8 Hz, 1H, aromatic), 7.36 (d, J = 8.3 Hz, 2H, aromatic), 7.44 (d, J = 8.6 Hz, 2H, aromatic), 8.09 (d, J = 9.4 Hz, 1H, -NHP). MS (FAB) m/z 645. Anal. (C, H, N) C₂₇H₄₁N₄O₈S₂P HCl.

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Example 642-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl}acetamide (21)

With stirring at 25 °C under N₂, DCC (0.160 g, 0.79 mmol) was added to a mixture of 2-nitrophenylacetic acid (0.140 g, 0.79 mmol) and pyridine (0.064 mL, 0.79 mmol) in CH₂Cl₂ (1.5 mL). After 3 min, a solution of **20** (0.160 g, 0.72 mmol) in CH₂Cl₂ (1.5 mL) was added, followed by NEt(iPr)₂ (0.375 mL, 2.15 mmol). The mixture was stirred at 25 °C under N₂ overnight before sat'd NaHCO₃ was added, and the mixture was filtered through celite. The DCU was washed with a little CH₂Cl₂, and the filtrate was partitioned between sat'd NaHCO₃ and CH₂Cl₂, which was dried (MgSO₄), filtered through celite, and evaporated. Toluene was added to azeotrope off pyridine. The product was flash column chromatographed eluting with CHCl₃:2% NH₃:2% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from MeOH to yield **21**·HCl (0.14 g, 47%): m.p. (HCl salt) 226-227 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.8-2.4 (m, 2H, -CH₂), 2.86 (s, 3H, -NCH₃), 3-4.5 (complex, 8H, 4 -CH₂-), 5.5 (m, 1H, -CHOH), 6.1 (m, 1H, -CH-), 7.3-7.8 (complex, 8H, aromatic), 8.11 (d, J = 8 Hz, 1H, aromatic). MS (FAB) m/z 384. Anal. (C, H, N) C₂₁H₂₅N₃O₄·HCl·0.5H₂O.

Example 652-(2-Nitro-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl}acetamide (22)

This compound was prepared from **20** (0.2 g, 0.91 mmol), 2-nitro-4,5-dichlorophenylacetic acid (0.45 g, 1.8 mmol), DCC (0.37 g, 1.8 mmol), NEt(iPr)₂ (0.48 mL, 2.7 mmol), and pyridine (0.15 mL, 1.8 mmol). The conditions are similar to those for the preparation of **21**. The product was column chromatographed eluting with CH₂Cl₂:2% NH₃:1% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and crystallized from iPrOH to yield **22**·HCl (0.060 g, 14%): m.p. (HCl salt) 231-233 °C (dec); ¹H NMR (HCl salt, DMSO-d₆) δ 1.8-2.4 (m, 2H, -CH₂-), 2.85 (s, 3H, -NCH₃), 3.1-4.5 (complex, 8H, 4 -CH₂-), 5.5 (m, 1H, -CHOH), 6.1 (m, 1H, -CH-), 7.2-7.5 (m, 5H, aromatic), 7.88 (s, 1H, aromatic), 8.42 (s, 1H, aromatic). MS (FAB) m/z 452. Anal. (C, H, N) C₂₁H₂₃N₃O₄Cl₂·HCl.

Example 662-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide (25)

5 This compound was prepared from **20** (0.2 g, 0.91 mmol), 4-methylsulfonylphenylacetic acid (0.41 g, 1.8 mmol), DCC (0.37 g, 1.8 mmol), pyridine (0.15 mL, 1.8 mmol), and NEt(iPr)₂ (0.48 mL, 2.7 mmol). The conditions are similar to those for the preparation of **21**. After stirring at 25 °C overnight, more pyridine (0.075 mL, 0.9 mmol) and DCC (0.18 g, 0.9 mmol) were added, and the reaction was worked up the next day. The product was purified by radial

10 chromatography eluting with CH₂Cl₂:2% NH₃:1% MeOH before it was converted to the HCl salt with 1.0 M HCl in Et₂O and washed with hot iPrOH to yield **25**HCl (0.15 g, 36%): m.p. (HCl salt) 240-241 °C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.8-2.4 (m, 2H, -CH₂-), 2.8 (d, 3H, -NCH₃ of cis and trans amide rotamers), 3.23 (s, 3H, -SO₂CH₃), 3.1-4.5 (m, 8H, 4 -CH₂-), 5.5 (m, 1H, -CHOH), 6.15 (m, 1H, -CH-), 7.2-7.5 (m, 5H, aromatic), 7.55 (m, 2H, aromatic), 7.85 (m, 2H, aromatic). MS (FAB) m/z 417. Anal. (C, H, N) C₂₂H₂₈N₂O₄S·HCl.

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Example 672-(2-Nitro-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)]ethyl]acetamide (26)

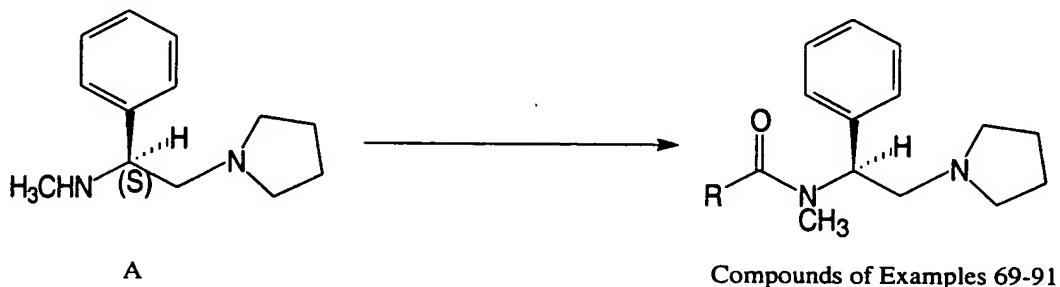
20 With stirring at 25 °C under N₂, DCC (0.39 g, 1.9 mmol) was added to a mixture of 2-nitro-4-trifluoromethylphenylacetic acid (0.47 g, 1.9 mmol) and pyridine (0.15 mL, 1.9 mmol) in CH₂Cl₂ (10 mL). After 5 min, a solution of **20** (0.4 g, 1.8 mmol) in CH₂Cl₂ (5 mL) was added. After 2 h, more DCC (0.1 g, 0.5 mmol) was added, and the mixture was stirred at 25 °C overnight

25 before more 2-nitro-4-trifluoromethylphenylacetic acid (0.045 g, 0.18 mmol) and DCC (0.1 g, 0.5 mmol) were added. After 2 h, the reaction was worked up as in the preparation of **21**. The product was purified by radial chromatography eluting with CH₂Cl₂:2% NH₃ before it was converted to the HCl salt with 1.0 M HCl in Et₂O and precipitated from CH₂Cl₂ to yield **26**HCl (0.050 g, 5.4%): ¹H NMR (HCl salt, DMSO-d₆) δ 1.8-2.4 (m, 2H, -CH₂-), 2.87 (s, 3H, -NCH₃), 3.1-4.5 (complex, 8H, 4 -CH₂-), 5.5 (m, 1H, -CHOH), 6.1 (m, 1H, -CH-), 7.2-7.5 (m, 5H, aromatic), 7.82 (d, J = 7.7 Hz, 1H, aromatic), 8.16 (d, J = 8 Hz, 1H, aromatic), 8.42 (s, 1H, aromatic). MS (FAB) m/z 452. Anal. (C, H, N) C₂₂H₂₄F₃N₃O₄·HCl·0.5H₂O.

Example 68**2-(2-Amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]acetamide (27)**

5 This compound was prepared from **26** (0.14 g, 0.31 mmol), Raney nickel, and hydrazine hydrate (0.2 mL) in EtOH (14 mL). The conditions were similar to those used for the preparation of **9**. The product was purified by radial chromatography eluting with CHCl₃:2% NH₃:2% MeOH before it was converted to the HCl salt with Et₂O-HCl to yield **27**·HCl (0.11 g, 77%): ¹H NMR (DMSO-d₆) δ 1.8-2.2 (m, 2H, -CH₂-), 2.88 (s, 3H, -NCH₃), 3.1-4.5 (complex, 9H, 4 -CH₂- and 1 -CHOH), 6.2 (m, 1H, -CH-), 6.8-7.5 (complex, 8 H, aromatic). MS (FAB) m/z 423. Anal. (C, H, N) C₂₂H₂₆N₃O₂F₃·HCl·2.5H₂O.

10 Compounds of Examples 69-91 were prepared from the appropriate arylacetic acids/acid chlorides via EDCI/DIPEA or DCC/pyridine couplings, followed by reduction, deprotection, and/or derivatization via known chemistry. Intermediate A was prepared via the method reported
15 in J. Med. Chem., **34**, 1991 pp. 181-189, Costello, G.F. et al.



General procedure for EDCI/DIPEA coupling.

To a solution of acid(1.1eq.) and 1-Hydroxybenzotriazole hydrate(HOBT;1.1eq.) in dry
20 CH₂Cl in an ice-bath under N₂ was added 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI;1.1eq.). The mixture was stirred for 30 minutes. A solution of the amine(1.0 eq.) in dry methylene chloride was added drop-wise followed by N,N-Diisopropylethylamine (DIPEA;1.5eq.). The solution was allowed to stir at room temperature overnight. The reaction was quenched with sat. sodium bicarbonate and separated from
25 methylene chloride. The organic layer was dried (Na₂SO₄), filtered through Celite, and evaporated. The crude product was chromatographed and converted to the HCl salt.

Example 692,2-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

To a solution of Diphenylacetic acid (1.5g; 7.3mmol) and pyridine (1.0mL; 12.2mmol) in 5 20mL of dry methylene chloride at 25 degrees under N₂ was added 1,3 dicyclohexylcarbodiimide, DCC (2.0g; 9.8mmol). After 5 minutes, **28**(1.0g; 4.9mmol) in 20mL of dry methylene chloride was added and the mixture was stirred overnight. TLC(95:5 methylene chloride:methanol with 2% ammonia) indicated all of the starting material was consumed. The reaction was quenched with sat. sodium bicarbonate and filtered through a Celite plug. The plug was rinsed with 10 methylene chloride and the aqueous layer was extracted with methylene chloride. The combined organic layers were dried (Na₂SO₄), filtered and concentrated *in vacuo* to give 2.2g of a light brown solid. The crude product was purified by flash chromatography using a stepwise gradient of 2% to 8% MeOH: methylene chloride with 2% ammonia to afford 1.7g(88%) of pure product which was treated with 1.0M HCl in diethyl ether to give **29** as the HCl salt. ¹H NMR (HCl salt, 15 DMSO-d₆) δ 2.0(br s, 4H, -CH₂CH₂-), 2.7(s, 3H, -NCH₃), 6.2(br m, 1H, -CH-), 7.1-7.5(complex, 15H, aromatic). MS (FAB) m/z 398. Anal.(C,H,N) C₂₇H₃₀N₂O.HCl.0.75H₂O.

Example 70N',N'-Diphenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]urea

20 To a 0 degree solution of **28** (500mg; 2.4mmol) and triethylamine(731mL; 5.2mmol) in 10mL of dry methylene chloride under N₂ was added a solution of Diphenylcarbamyl chloride(629mg; 2.7mmol) in 5mL of dry methylene chloride. The solution was warmed to room temperature and stirred overnight. TLC(95:5 methylene chloride: methanol with 2% ammonia) indicated the starting material was consumed. The reaction solution was concentrated to a residue, which was pre-adsorbed onto silica and purified using a stepwise gradient of 2% to 7% MeOH: methylene chloride with 2% ammonia to afford 350mg(36%) of pure product which was treated with 1.0M HCl in diethyl ether to give **30** as the HCl salt. ¹H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.5(s, 3H, -NCH₃), 5.8(br,m,1H, -CH-), 7.1-7.5(complex, 15H, aromatic). MS(FAB) m/z 399. Anal.(C,H,N) C₂₆H₂₉N₃O.HCl.0.5H₂O.

Example 712-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the procedure described in the preparation of 29 from 28
5 (0.6g;2.9mmol), 2-nitrophenylacetic acid (0.8g;4.4mmol), DCC(1.2g;5.8mmol), and
pyridine(0.1mL;1.4mmol). The crude product was purified by flash chromatography using a
stepwise gradient of 2% to 7% MeOH: methylene chloride with 2% ammonia to afford
0.2g(20%) of pure product which was treated with 1.0M HCl in diethyl ether to give 31 as the
HCl salt. ^1H NMR(HCl salt, DMSO-d₆) δ 2.0(br s, 4H, -CH₂CH₂-), 2.9(s, 3H, -NCH₃), 6.1(br,m,
10 1H, -CH-)7.3-8.1(complex, 9H, aromatic). MS(FAB) m/z 367. Anal. (C,H,N) C₂₁H₂₅N₃O₃.HCl.

Example 722-(2-Nitro- 4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

15 This compound was prepared via the general EDCI/DIPEA coupling procedure from 28
(1.4g; 6.9mmol), 2-nitro 4,5-dichlorophenylacetic acid (1.9g; 7.6mmol), HOBT (1.0g;7.6mmol),
EDCI(1.4g;7.6mmol), and pyridine(0.8mL;10.3mmol). The crude product was purified by flash
chromatography using a stepwise gradient of 2% to 5% MeOH: methylene chloride with 2%
20 ammonia to afford 2.0g(60%) of pure product which was treated with 1.0M HCl in diethyl ether
to give 32 as the HCl salt. ^1H NMR(HCl salt, DMSO-d₆) δ 2.0(br, s, 4H, -CH₂CH₂-), 2.9(s, 3H, -
NCH₃), 6.1(br, m, 1H, -CH-), 7.2-7.6(complex, 5H, aromatic), 7.9(s, 1H, aromatic), 8.4(s, 1H,
aromatic). MS(FAB) m/z 436. Anal. (C,H,N) C₂₁H₂₃N₃O₃Cl₂.HCl.0.25 H₂O.

Example 732-(4-Methylsulfonylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

25 This compound was prepared via the general EDCI/DIPEA coupling procedure from 28
(432 mg; 2. mmol), 4-Methylsulfonylphenylacetic acid (500 mg; 2.3 mmol), HOBT (341 mg; 2.5
30 mmol), EDCI (483 mg; 2.5 mmol),and DIPEA (0.550 mL; 3.1 mmol). The crude product was
purified by flash chromatography using a stepwise gradient of 2% to 4% MeOH: methylene
chloride with 2% ammonia to afford 160 mg (19%) of pure product which was treated with 1.0M
HCl in diethyl ether to give 33 as the HCl salt. ^1H NMR (HCl salt, DMSO-d₆) δ 2.0 (br, s, 4H, -
CH₂CH₂-), 2.9 (s, 3H, -NCH₃), 3.2 (s, -SO₂CH₃), 6.1 (br, m, 1H, -CH-), 7.3-7.5 (complex, 5H,

aromatic), 7.6 (br, d, 2H, aromatic), 7.9 (br, d, 2H, aromatic). MS (FAB) m/z 400. Anal. (C,H,N) C₂₂H₂₈N₂O₃S.HCl.0.5 H₂O.

Example 74

2-(2-Methoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28** (500 mg; 2.4 mmol), 2-Methoxyphenylacetic acid (610 mg; 3.6 mmol), HOBT (495 mg; 3.6 mmol), EDCI (700 mg; 3.6 mmol), and DIPEA (0.850 mL; 4.8 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 7% MeOH: methylene chloride with 2% ammonia to afford 822mg(96%) of pure product which was treated with 1.0M HCl in diethyl ether to give **34** as the HCl salt. ¹H NMR (free base, CDCl₃) δ1.8 (br, s, 4H, -CH₂CH₂-), 2.8 (s, 3H, -NCH₃), 3.8 (s, 3H, OCH₃), 6.1 (br, m, 1H, -CH-), 6.8-7.4 (complex, 9H, aromatic). MS (FAB) m/z 352. Anal. (C,H,N) C₂₂H₂₈N₂O₂.HCl.

15

Example 75

2-(3-Indolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28** (500 mg; 2.4 mmol), Indole-3-acetic acid (641 mg; 3.6 mmol), HOB (494 mg; 3.6 mmol), EDCI (700 mg;3.6 mmol),and DIPEA (0.637 mL;3.6 mmol).The crude product was purified by flash chromatography using a stepwise gradient of 1% to 7% MeOH: methylene chloride to afford 761mg (88%) of pure product which was treated with 1.0M HCl in diethyl ether to give **35** as the HCl salt. ¹H NMR (HCl salt, CD₃OD) δ 2.1 (br, s, 4H, -CH₂CH₂-), 2.8 (s, 3H, -NCH₃), 6.3 (br, m, 1H, -CH-), 7.1-7.7 (complex, 9H, aromatic). MS (FAB) m/z 361. Anal. (C,H,N) C₂₃H₂₇N₃O.HCl.1.0 H₂O.

Example 76

2-(α,α,α -Trifluoro-p-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

30

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28** (200 mg; 0.9 mmol), (α,α,α -Trifluoro-p-tolyl) acetic acid (239 mg; 1.1 mmol), HOBT (157 mg; 1.1 mmol), EDCI (223 mg; 1.1 mmol), and DIPEA (0.203 mL; 1.1mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 2% MeOH: methylene chloride to afford 354mg (93%) of pure product which was treated with 1.0M HCl in diethyl

ether to give 36 as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 1.8 (br, s, 4H, $-\text{CH}_2\text{CH}_2-$), 3.0 (s, 3H, NCH_3), 6.4 (br, m, 1H, CH), 7.2-7.6 (complex, 9H, aromatic). MS (FAB) m/z 390. Anal. (C,H,N) $\text{C}_{22}\text{H}_{25}\text{N}_2\text{OF}_3\text{.HCl}$.

5

Example 772-(2-Nitro- α,α,α -Trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from 28 (500 mg; 2.4 mmol), (2-Nitro- α,α,α -trifluoro-4-tolyl) acetic acid (728 mg; 2.9 mmol), OBT (395 mg; 2.9 mmol), EDCI (559 mg; 2.9 mmol), and DIPEA (0.510 mL; 2.9 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 10% MeOH:methylene chloride to afford 786mg (74%) of pure product which was treated with 1.0M HCl in diethyl ether to give 37 as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 2.0 (br, s, 4H, $-\text{CH}_2\text{CH}_2-$), 2.9 (s, 3H, $-\text{NCH}_3$), 6.3 (br, m, 1H, CH), 7.1-7.5 (complex, 4H, aromatic), 7.8-7.9 (br, m, 2H, aromatic), 8.3-8.4 (br, s, 2H, aromatic). MS (FAB) m/z 435. Anal. (C,H,N) $\text{C}_{22}\text{H}_{24}\text{N}_3\text{O}_3\text{F}_3\text{.HCl}$.

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Example 782-(1-[4-Chlorobenzoyl]-5-methoxy-2-methyl indole)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from 28 (100 mg; 0.4 mmol), (1-[p-chlorobenzoyl]-5-methoxy-2-methyl indole-3-acetic acid (189 mg; 0.5 mmol), HOBT (73 mg; 0.5 mmol), EDCI (101 mg; 0.5 mmol), and DIPEA (128 mL; 0.7 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 5% MeOH:methylene chloride to afford 200mg (79%) of pure product which was treated with 1.0M HCl in diethyl ether to give 38 as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 1.6-1.8 (br, m, 4H, $-\text{CH}_2\text{CH}_2-$), 2.3 (b, s, 3H, $-\text{CH}_3$), 2.9 (br, s, $-\text{NCH}_3$), 3.8 (br, s, 3H, $-\text{OCH}_3$), 6.7 (br, m, 1H, $-\text{CH}$), 7.1-7.6 (complex, 12H, aromatic). MS (FAB) m/z 509. Anal. (C,H,N) $\text{C}_{32}\text{H}_{35}\text{N}_3\text{O}_3\text{Cl}\text{.HCl}$.

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Example 792-(4-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from 28 (1.5 g; 7.3 mmol), 4-Nitrophenylacetic acid (2.0 g; 11.0 mmol), HOBT (1.4 g; 11.0 mmol), EDCI

(2.1 g; 11.0 mmol), and DIPEA (2.5 mL; 14.6 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 5% MeOH: methylene chloride to afford 2.5 g (93%) of pure product which was treated with 1.0M HCl in diethyl ether to give **39** as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 1.6 (br, m, 4H, $-\text{CH}_2\text{CH}_2-$), 2.8 (br, s, 3H, $-\text{NCH}_3$), 6.4 (br, m, 1H, $-\text{CH}$), 7.1-7.5 (complex, 7H, aromatic), 8.0 (br, d, 2H, aromatic). MS (FAB) m/z 367. Anal. (C,H,N) $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3\text{.HCl}$.

Example 80

2-(3-Nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

10 This compound was prepared via the general EDCI/DIPEA coupling procedure from **28** (1.5 g; 7.3 mmol), 3-Nitrophenylacetic acid (2.0 g; 11.0 mmol), HOBT (1.4g; 11.0mmol), EDCI (2.1g; 11.0 mmol), and DIPEA (2.5 mL; 14.6 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 5% MeOH:methylene chloride with 2% ammonia to afford 2.6 g (100%) of pure product which was treated with 1.0M HCl in diethyl ether to give **40** as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 2.0 (br, m, 4H, $-\text{CH}_2\text{CH}_2-$), 2.9 (br, s, 3H, $-\text{NCH}_3$), 6.3 (br, m, 1H, $-\text{CH}$), 7.2-7.6 (complex, 6H, aromatic), 7.8 (br, d, 1H, aromatic), 8.1-8.2 (complex, 2H, aromatic). MS (FAB) m/z 367. Anal. (C,H,N) $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_3\text{.HCl}$. 0.5 H_2O .

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Example 81

2-(2-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28** (350 mg; 1.7 mmol), 2-Pyridylacetic acid hydrochloride (326 mg; 1.8 mmol), HOBT (253 mg; 1.8 mmol), EDCI (360 mg; 1.8 mmol) and DIPEA (0.644 mL; 3.7 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 5% MeOH: methylene chloride with 2% ammonia to afford 400 mg (72%) of pure product which was treated with 1.0M HCl in diethyl ether to give **41** as the HCl salt. ^1H NMR (free base, CDCl_3) δ 1.7-1.9 (br, m, 4H, $-\text{CH}_2\text{CH}_2$), 2.8 (br, s, 3H, $-\text{NCH}_3$), 6.0-6.2 (br, m, 1H, $-\text{CH}$), 7.1-7.8 (complex, 8H, aromatic), 8.5 (br, d, 1H, aromatic). MS (FAB) m/z 323. Anal. (C,H,N) $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_2\text{.2 HCl}$. 0.5 H_2O .

Example 822-(3-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from 28 (120 mg; 0.5m mol), 3-Pyridylacetic acid hydrochloride (110 mg; 0.6 mmol), HOBT (85 mg; 0.6 mmol), EDCI (120 mg; 0.6 mmol), and DIPEA (0.280 mL; 1.5 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 6% MeOH:methylene chloride with 2% ammonia to afford 142 mg (76%) of pure product which was treated with 1.0M HCl in diethyl ether to give 42 as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 2.1 (br, m, 4H, - CH_2CH_2-), 2.9 (br, s, 3H, - NCH_3), 6.2-6.3 (br, m, 1H, - CH), 7.2-7.3 (complex, 5H, aromatic), 7.8-7.9 (br, t, 1H, aromatic), 8.6-8.9 (complex, 3H, aromatic). MS (FAB) m/z 323. Anal. (C,H,N) $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O} \cdot 0.2 \text{ HCl} \cdot 1.25 \text{ H}_2\text{O}$.

Example 832-((+)-6-Methoxy-a-methyl-2-naphthalene)-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from 28 (200 mg; 0.9 mmol), (+)-6-Methoxy- α -methyl-2-naphthaleneacetic acid (217 mg; 1.0 mmol), HOBT (142 mg; 1.0 mmol), EDCI (201 mg; 1.0 mmol), and DIPEA (0.256 mL; 1.4 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 2% MeOH:methylene chloride with 2% ammonia to afford 130mg (33%) of pure product which was treated with 1.0M HCl in diethyl ether to give 43 as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 1.4 (d, 3H, - CH_3), 2.9 (br, s, - NCH_3), 3.9 (s, - OCH_3), 5.5 (br, m, 1H, - CH), 7.0-7.7 (complex, 11H, aromatic). MS (FAB) m/z 416. Anal. (C,H,N) $\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2 \cdot \text{HCl} \cdot 0.25 \text{ H}_2\text{O}$.

Example 842-(α,α,α -Trifluoro-3-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from 28 (200 mg; 0.9 mmol), (α,α,α -Trifluoro-m-tolyl) acetic acid (214 mg; 1.0 mmol), HOBT (142 mg; 1.0 mmol), EDCI (201 mg; 1.0 mmol), and DIPEA (0.256 mL; 1.4 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 6% MeOH:methylene chloride to afford 250mg (67%) of pure product which was treated with 1.0M HCl in diethyl ether to give 44 as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 2.0 (br, m, 4H, - CH_2CH_2-), 2.9 (br,

s, 3H, -NCH₃), 6.4 (br, m, 1H), 7.1-7.7 (complex, 9H, aromatic). MS (FAB) m/z 390. Anal. (C,H,N) C₂₂H₂₅N₂OF₃.HCl.

Example 85

2-(4-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28**

(120 mg; 0.5 mmol), 4-Pyridylacetic acid hydrochloride (150 mg; 0.8 mmol), HOBT (117 mg; 0.8 mmol), EDCI (166 mg; 0.8 mmol), and DIPEA (0.202 mL; 1.1 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 5% MeOH:methylene chloride to afford 172mg (92%) of pure product which was treated with 1.0M HCl in diethyl ether to give **45** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 2.1 (br, m, 4H, -CH₂CH₂-), 2.9 (br, s, -NCH₃), 6.3 (br, m, -CH), 7.2-7.3 (complex, 5H, aromatic), 7.8 (br, s, 2H, aromatic), 8.6 (br, s, 2H, aromatic). MS (FAB) m/z 323. Anal. (C,H,N) C₂₀H₂₅N₃O.1.5 HCl. 0.5 H₂O.

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Example 86

2-(α,α,α -Trifluoro-2-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28**

(200 mg; 0.9 mmol), (α,α,α -Trifluoro-*o*-tolyl)acetic acid (239 mg; 1.1 mmol), HOBT (157 mg; 1.1 mmol), EDCI (223 mg; 1.1 mmol), and DIPEA (0.203 mL; 1.1 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 4% MeOH:methylene chloride with 2% ammonia to afford 339 mg (82%) of pure product which was treated with 1.0M HCl in diethyl ether to give **46** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 2.0 (br, m, 4H-CH₂CH₂-), 2.9 (br, s, -NCH₃), 6.3 (br, m, 1H, -CH), 7.1-7.7 (complex, 9H, aromatic). MS (FAB) m/z 390. Anal. (C,H,N) C₂₂H₂₅N₂OF₃. HCl.

Example 87

2-((S)-(+)-4-Isobutyl- α -methylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

This compound was prepared via the general EDCI/DIPEA coupling procedure from **28**

(200 mg; 0.9 mmol), (S)-(+)-4-Isobutyl- α -methylphenylacetic acid (217 mg; 1.0 mmol), HOBT (142 mg; 1.0 mmol), EDCI (201 mg; 1.0 mmol), and DIPEA (0.256 mL; 1.4 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 1% to 2%

MeOH:methylene chloride with 2% ammonia to afford 240mg (66%) of pure product which was treated with 1.0M HCl in diethyl ether to give **47** as the HCl salt. ^1H NMR (HCl salt, CDCl_3) δ 0.8 (d, 6H, -(CH_3)₂), 1.4 (d, 2H, - CH_3), 2.0 (br, m, - CH_2CH_2 -), 2.3-2.4 (d, 2H, - CH_2 -), 2.9 (s, 3H, - NCH_3), 5.6 (br, m, 1H, - CH), 7.0 (br, q, 4H, aromatic), 7.3 (br, s, 5H, aromatic). MS (FAB) 5 m/z 392. Anal. (C, H, N) $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}$. HCl. 0.25 H_2O .

Example 88

2-(3,4,5-Trimethoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

10 This compound was prepared via the general EDCI/DIPEA coupling procedure from **28** (250 mg; 1.2 mmol), 3,4,5-Trimethoxyphenylacetic acid (304 mg; 1.3 mmol), HOBT (181 mg; 1.3 mmol), EDCI (256 mg; 1.3 mmol), and DIPEA (0.318 mL; 1.8 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 5% MeOH:methylene chloride with 2% ammonia to afford 500 mg (100%) of pure product which was treated with 15 1.0M HCl in diethyl ether to give **48** as the HCl salt. ^1H NMR (free base, CDCl_3) δ 1.7 (br, m, 4H, - CH_2CH_2 -), 2.7 (s, 3H, - NCH_3), 3.8 (d, 9H, - OCH_3), 6.0-6.2 (br, m, 1H, - CH), 6.4 (s, 2H, aromatic), 7.1-7.3 (complex, 5H, aromatic). MS (FAB) m/z 412. Anal. (C,H,N) $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_4\text{.HCl}$.

Example 89

2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

20 Raney-Nickel(50% slurry in water) was added to a mixture of **31** (2.30 g; 6.1 mmol), 2.2 mL (61.9 mmol) of hydrazine hydrate and 45 mL of abs. EtOH at 55 degrees to maintain a regular gas evolution. After 45 min., TLC (95:5 methylene chloride:methanol w/2% ammonia) indicated that all of the starting material was consumed. The mixture was filtered through a 25 Celite plug and rinsed with copious amounts of hot methanol. The filtrates were combined and concentrated *in vacuo* to afford 270 mg of a waxy solid. The crude product was purified by flash chromatography using a stepwise gradient of 1% to 8% methanol:methylene chloride with 2% ammonia to afford 2.01g (97%) of desired product. The pure product was treated with 1.0M HCl 30 in diethyl ether to yield **49** as the HCl salt. ^1H NMR (HCl salt, DMSO-d_6) δ 2.0 (br, m, 4H, - CH_2CH_2 -), 2.9 (s, 3H, - NCH_3), 6.1 (br, m, 1H, - CH), 7.2 (complex, 9H, aromatic). MS (FAB) m/z 321. Anal. (C,H,N) $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}$. 2HCl. 0.75 H_2O .

Example 902-(2-N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

5 To a solution of **49** (400 mg; 1.1 mmol) in 50 ml of dry methylene chloride was added 429mL of triethylamine and MsCl (913 mL; 11.8 mmol) dissolved in 6 mL of dry methylene chloride. The dark red solution was allowed to stir overnight. TLC (95:5 methylene chloride:methanol w/2% ammonia) indicates the starting material is consumed. The reaction solution was quenched with sat. sodium bicarbonate and the layers were separated. The aqueous 10 layer was extracted with methylene chloride and the combined organic layers were dried over anh. sodium sulfate, filtered and the solvent was concentrated *in vacuo* to give 700 mg of a dark brown residue. The crude product was purified by flash chromatography using a stepwise gradient of 2% to 7% methanol:methylene chloride with 2% ammonia to afford 580 mg (97%) of desired product. The pure product was treated with 1.0M HCl in diethyl ether to yield **50** as the 15 HCl salt. ^1H NMR (HCl salt, DMSO-d₆) δ 2.0 (br, m, 4H, -CH₂CH₂-), 2.7 (br, s, 3H, -NCH₃), 3.5 (br, s, (-SO₂CH₃)₂), 6.2 (br, d, 1H, -CH), 7.2-7.5 (complex, 9H, aromatic). MS (FAB) m/z 493. Anal. (C,H,N) C₂₃H₃₁N₃O₅S₂.HCl. 0.25 H₂O.

Example 912-(N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

20 To a solution of **50** (500 mg; 1.0 mmol) in 6 mL of 2:1 MeOH:THF was added 4.0mL of 1.0M NaOH. The solution was stirred for 20 min., after which TLC (95:5 methylene chloride:methanol w/2% ammonia) indicates the reaction is complete. The reaction was 25 quenched with 10% HCl and washed with water and brine. The organic layer was dried over anh. sodium sulfate, filtered and concentrated *in vacuo* to give 381 mg of a brown solid. The crude product was purified by flash chromatography using a stepwise gradient of 2% to 4% methanol:methylene chloride with 2% ammonia to afford 326 mg (80%) of desired product. The pure product was treated with 1.0M HCl in diethyl ether to yield **51** as the HCl salt. ^1H NMR (HCl 30 salt, CDCl₃) δ 2.0 (br, m, 4H, -CH₂CH₂-), 2.9 (br, s, 3H, -NCH₃), 3.0 (s, 3H, -SO₂CH₃), 6.3 (br, m, 1H, -CH), 7.0-7.2 (complex, 8H, aromatic), 7.5 (br, d, 1H, aromatic). MS (FAB) m/z 415. Anal. (C,H,N) C₂₂H₂₉N₃O₃S.HCl. 0.25 H₂O.

Example 922-(2-Amino4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

5 To a solution of **32** (495 mg; 1.0 mmol) in 25 mL of abs. EtOH was added 50 mg of 10% Pd/C. The mixture was placed on a Parr apparatus under 10psi of hydrogen. After 1h, TLC (95:5 methylene chloride:methanol) indicates no starting material remains. The mixture was filtered through a Celite plug and basified with aq. ammonium hydroxide. The solvent was concentrated *in vacuo* to get a residue which was dissolved in EtOAc and washed repeatedly with water. The 10 organic layer was dried over anh. sodium sulfate, filtered and concentrated to give 200 mg of crude free base. The crude product was treated with 1.0M HCl in diethyl ether and dried in a vacuum oven at 80 degrees overnight to recover 120 mg (30%) of **52** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 1.6-1.7 (br, m, 4H, -CH₂CH₂-), 2.7 (s, 3H, -NCH₃), 5.9-6.1 (br, m, 1H, -CH), 7.1-7.2 (complex, 7H, aromatic). MS (FAB) m/z 406. Anal. (C,H,N) C₂₁H₂₅N₃OCl₂.HCl. 1.5 15 H₂O.

Example 932-(N,N-Dimethylsulfonamido-2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

20 Same procedure as **50** using 223 mg (0.54 mmol) of **52**, 0.5 mL (6.4 mmol) of MsCl, 2.0 mL (14.3 mmol) of triethylamine and 25 mL of dry methylene chloride. The crude product was purified by flash chromatography using a stepwise gradient of 1% to 3% MeOH: methylene chloride to yield 150 mg (49%) of pure product which was treated with 1.0M HCl in diethyl ether to give **53** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 2.0 (br, m, 4H, -CH₂CH₂-), 2.8 (s, 3H, NCH₃), 3.3 (d, 6H, -(SO₂CH₃)₂), 6.2 (br, m, 1H, -CH), 7.0-7.1 (complex, 2H, aromatic), 7.3 (complex, 5H, aromatic). MS (FAB) m/z 562. Anal. (C,H,N) C₂₃H₂₉N₃O₅S₂Cl₂. HCl. 0.5 H₂O.

Example 942-(2-Amino,α,α,α-Trifluoro-4-toly)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

30 Same procedure as **49** using 710 mg (1.6 mmol) of **37**, 0.5mL (16.3 mmol) of hydrazine hydrate in 50mL of EtOH. The recovered product, 650 mg (98% crude recovery) was not purified any further. A small amount of the desired product was treated with 1.0M HCl in diethyl ether to form **54** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 2.0 (br, m, 4H, -CH₂CH₂-), 2.9

(br, s, 3H, -NCH₃), 6.3 (br, m, 1H, -CH), 7.2-7.5 (complex, 8H, aromatic). MS (FAB) m/z 405. Anal. (C,H,N) C₂₂H₂₆N₃OF₃ 1.5 HCl.

Example 95

5 2-(2-N,N-Dimethylsulfonamido-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

Same procedure as **50** using 100 mg (0.24 mmol) of **54**, 0.2 mL (2.4 mmol) of MsCl, 0.8 mL (6.3 mmol) of triethylamine and 13 mL of dry methylene chloride. The crude product was 10 purified by flash chromatography using a stepwise gradient of 1% to 5% MeOH: methylene chloride to yield 110 mg (80%) of desired product. A small amount of compound was treated with 1.0M HCl in diethyl ether to give **55** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 2.0 (br, m, 4H, -CH₂CH₂-), 2.9 (s, 3H, -NCH₃), 3.3 (d, 6H, -(SO₂CH₃)₂), 6.3 (br, m, 1H, -CH), 7.1-8.0 (complex, 8H, aromatic). MS (FAB) m/z 497. Anal. (C,H, N) C₂₄H₃₀N₃OF₃S₂. HCl. 0.5 H₂O.

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Example 96

20 2-(N-Methylsulfonamido-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

Same procedure as **51** using 51 mg (0.1 mmol) of **55**, 30 mL of 1.0M NaOH and 1.9 mL of 20 2:1 MeOH:THF. The crude product was purified by flash chromatography using a stepwise gradient of 1% to 5% MeOH: methylene chloride with 2% ammonia to yield 27 mg (63%) of pure product which was treated with 1.0 M HCl in diethyl ether to form **56** as the HCl salt. ¹H NMR (HCl salt, CDCl₃) δ 2.0 (br, m, 4H, -CH₂CH₂-), 2.9 (br, s, 3H, -NCH₃), 3.1 (br, s, 3H, -SO₂CH₃), 7.1-7.3 (complex, 8H, aromatic). MS (FAB) m/z 483. Anal. (C,H,N) 25 C₂₃H₂₈N₃O₃SF₃.HCl. 0.25 H₂O.

Example 97

30 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

Same procedure as **49** using 2.6 g (7.1 mmol) of **40**, 2.5 mL (80.2 mmol) of hydrazine hydrate in 70 mL of EtOH. The recovered product, 1.8 g was purified by flash chromatography using a stepwise gradient of 1% to 9% MeOH: methylene chloride with 2% ammonia to yield 1.1 g (47%) of pure product which was treated with 1.0 M HCl in diethyl ether to give **57** as the HCl salt. ¹H NMR (free base, CDCl₃) δ 1.7-1.9 (br, m, 4H, -CH₂CH₂-), 2.7 (s, 3H, -NCH₃), 6.1 (br, 35

m, 1H, -CH), 6.5-6.8 (complex, 3H, aromatic), 7.0 (m, 2H, aromatic), 7.3 (complex, 4H, aromatic). MS (FAB) m/z 337. Anal. (C₂₁H₂₇N₃O). 2HCl. 0.5 H₂O.

Example 98

2-(4-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

Same procedure as **49** using 2.3 g (6.3 mmol) of **39**, 2.4 mL (75.4 mmol) of hydrazine hydrate in 70 mL of EtOH. The recovered product, 1.7 g was purified by flash chromatography using a stepwise gradient of 2% to 3% MeOH: methylene chloride with 2% ammonia to yield 1.53 g (73%) of pure product. A small amount of compound was treated with 1.0 M HCl in diethyl ether to give **58** as the HCl salt. ^1H NMR (free base, CDCl_3) δ 1.8 (br, m, 4H, $-\text{CH}_2\text{CH}_2-$), 2.7 (s, 3H, $-\text{NCH}_3$), 6.1 (br, m, 1H, $-\text{CH}$), 6.7 (m, 2H, aromatic), 7.0 (d, 2H, aromatic), 7.3 (complex, 5H, aromatic). MS (FAB) m/z 337. Anal. $(\text{C},\text{H},\text{N}) \text{C}_{21}\text{H}_{27}\text{N}_3\text{O} \cdot 2\text{HCl} \cdot 0.75 \text{ H}_2\text{O}$.

Example 99

2-(N,N-Dimethylsulfonamido-3-aminophenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-acetamide

Same procedure as **50** using 500 mg (1.5 mmol) of **57**, 1.1 mL (14.8 mmol) of MsCl, 3.0 mL (22.2 mmol) of triethylamine and 8.0 mL of dry methylene chloride. The crude product was purified by flash chromatography using a stepwise gradient of 1% to 4% MeOH: methylene chloride with 2% ammonia to yield 308 mg (42%) of pure product. A small amount of compound was treated with 1.0 M HCl in diethyl ether to give **59** as the HCl salt. ^1H NMR (free base, CDCl_3) δ 1.8 (br, m, 4H, $-\text{CH}_2\text{CH}_2-$), 2.8 (s, 3H, $-\text{NCH}_3$), 3.4 (s, 6H, $(-\text{SO}_2\text{CH}_3)_2$), 6.1 (br, m, 1H, $-\text{CH}$), 7.0-7.5 (complex, 9H, aromatic). MS (FAB) m/z 493. Anal. (C,H,N) $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_5\text{S}_2 \cdot \text{HCl}$

Example 100

(2-(N,N-Dimethylsulfonamido-4-aminophenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide)

35 Same procedure as **50** using 400 mg (1.2 mmol) of **58**, 0.55 mL (7.1 mmol) of MsCl, 1.6 mL (11.8 mmol) of triethylamine and 12.0 mL of dry methylene chloride. The crude product was purified by flash chromatography using a stepwise gradient of 2% to 5% MeOH: methylene chloride with 2% ammonia to yield 395 mg (68%) of pure product. The compound was treated

with 1.0 M HCl in diethyl ether to give **60** as the HCl salt. ^1H NMR (free base, CDCl_3) δ 1.8 (br, m, 4H, - CH_2CH_2 -), 2.8 (s, 3H, - NCH_3), 3.4 (s, 6H, (- SO_2CH_3)₂), 6.1 (br, m, 1H, - CH), 7.0-7.5 (complex, 9H, aromatic). MS (FAB) m/z 493. Anal. (C,H,N) $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_5\text{S}_2\text{.HCl}$. 0.25 H_2O .

5

Example 101

2-(2-Hydroxyphenyl)-N-methyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

To a solution of **34** (700mg; 1.8mmol) in 10mL of dry methylene chloride @ 78°C was added 10.8 mL (10.8 mmol; 1.0M solution of BBr_3 in methylene chloride) over 15 minutes. The reaction mixture was allowed to warm to room temperature and stir overnight. TLC (95:5 methylene chloride: MeOH w/2% ammonia) indicated no starting material remained. The reactionn was quenched with the addition of MeOH at 0 degrees. After 30 minutes, 3N HCl was added and the mixture was stirred for 30 minutes (white precipitate seen). The mixture was made neutral with sat. bicarbonate and extracted with methylene chloride (3x100MmL). The organic layer was dried over anh. sodium sulfate, filtered and concentrated *in vacuo* to give 610mg of crude product. The crude product was purified by flash chromatography using a stepwise gradient of 2% to 3% MeOH: methylene chloride to yield 500 mg (82%) of pure product. The product was treated with 1.0 M HCl in diethyl ether to give **61** as the HCl salt. ^1H NMR (free base, CDCl_3) δ 1.7 (br, m, 4H, - CH_2CH_2 -), 2.9 (s, 3H, - NCH_3), 6.1 (br, m, 1H, - CH), 6.8-7.4 (complex, 9H, aromatic). MS (FAB) m/z 338. Anal. (C,H,N) $\text{C}_{21}\text{H}_{26}\text{N}_2\text{O}_2\text{.HCl}$. 0.5 H_2O .

25

Example 102

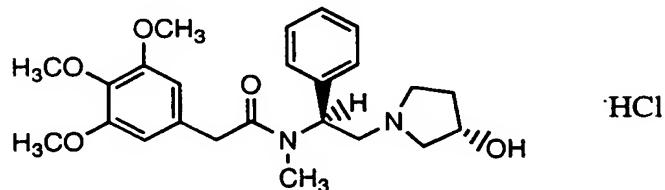
N-Methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidine-1-yl)ethyl]-3,4,5-trimethoxyphenylacetamide HCl

To a solution of 3,4,5-trimethoxyphenylaetic acid (1.0 g, 4.43 mmol) in 10 mL of CH_2Cl_2 under a nitrogen atmosphere was added pyridine (0.12 g, 1.5 mmol) and N,N-diisopropylethylamine (Hunig's Base) (0.57 g, 4.43 mmol). The reaction mixture was cooled to 0°C and DCC (1.37 g, 6.65 mmol) was added in one portion. The reaction mixture was stirred at this temperature and a solution of the diamine (0.65 g, 3.0 mmol) in 10mL of CH_2Cl_2 was added and the stirring was continued while warming to room temperature for 20 h. The reaction mixture was poured onto an aqueous saturated solutoin of NaHCO_3 and the mixture was stirred for 30 min. The organic layer was separated and dried over anhydrous Na_2SO_4 . After removal

of the solvent, the product was purified on a silica gel column [solvent system: CHCl_3 :
 CH_3OH :28% NH_4OH (98:2:2)]. The free base was converted to the hydrochloride salt from 1M
etherial HCl and recrystallized from CH_2Cl_2 : Et_2O (1:1) to give a HCl 0.64 g (46%) as light pink
solid; mp 230-232°C; $^1\text{H-NMR}$ (200 MHz, CDCl_3) δ 2.20 (m, 4H), 2.85 (s, 3H), 3.00-4.30 (m,
5H), 3.70 (ms, 9H), 4.50 (m, 2H), 5.30 (d, J = 15.0 Hz, 1H), 6.50 (m, 3H), 7.28 (m, 5H). Anal.
5 Calcd for $\text{C}_{24}\text{H}_{32}\text{N}_2\text{O}_5\text{.HCl.0.25H}_2\text{O}$: C, 61.40; H, 7.19; N, 5.97. Found: C, 61.36; H, 6.84; 8.96;
N, 5.91.

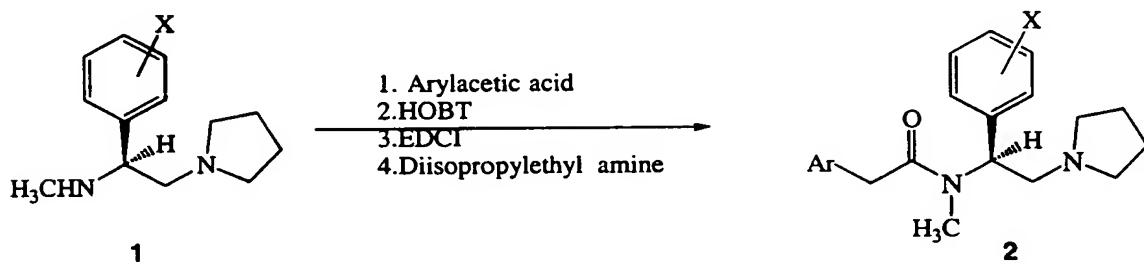
The structure of the compound is shown hereunder.

10

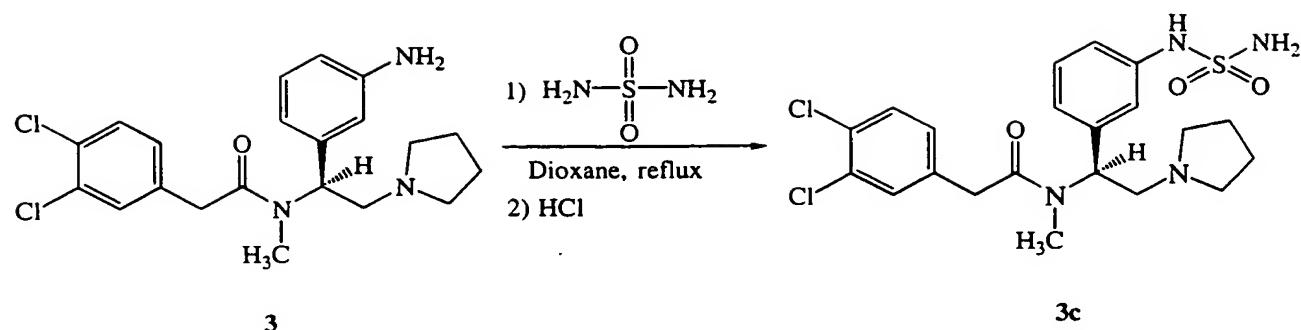


15 The preparation of compounds **3a** through **3ddd** of formula **IIIA** follow according to
Schemes G, H, I, J, K, L, M, and N.

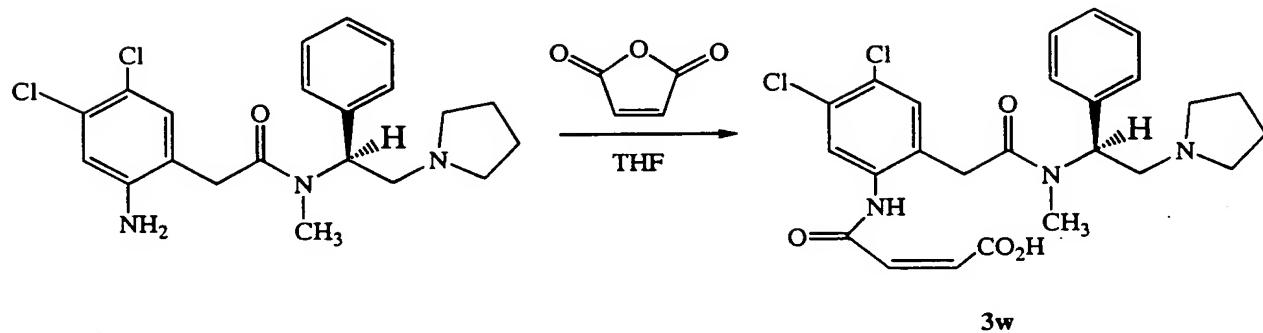
Scheme G

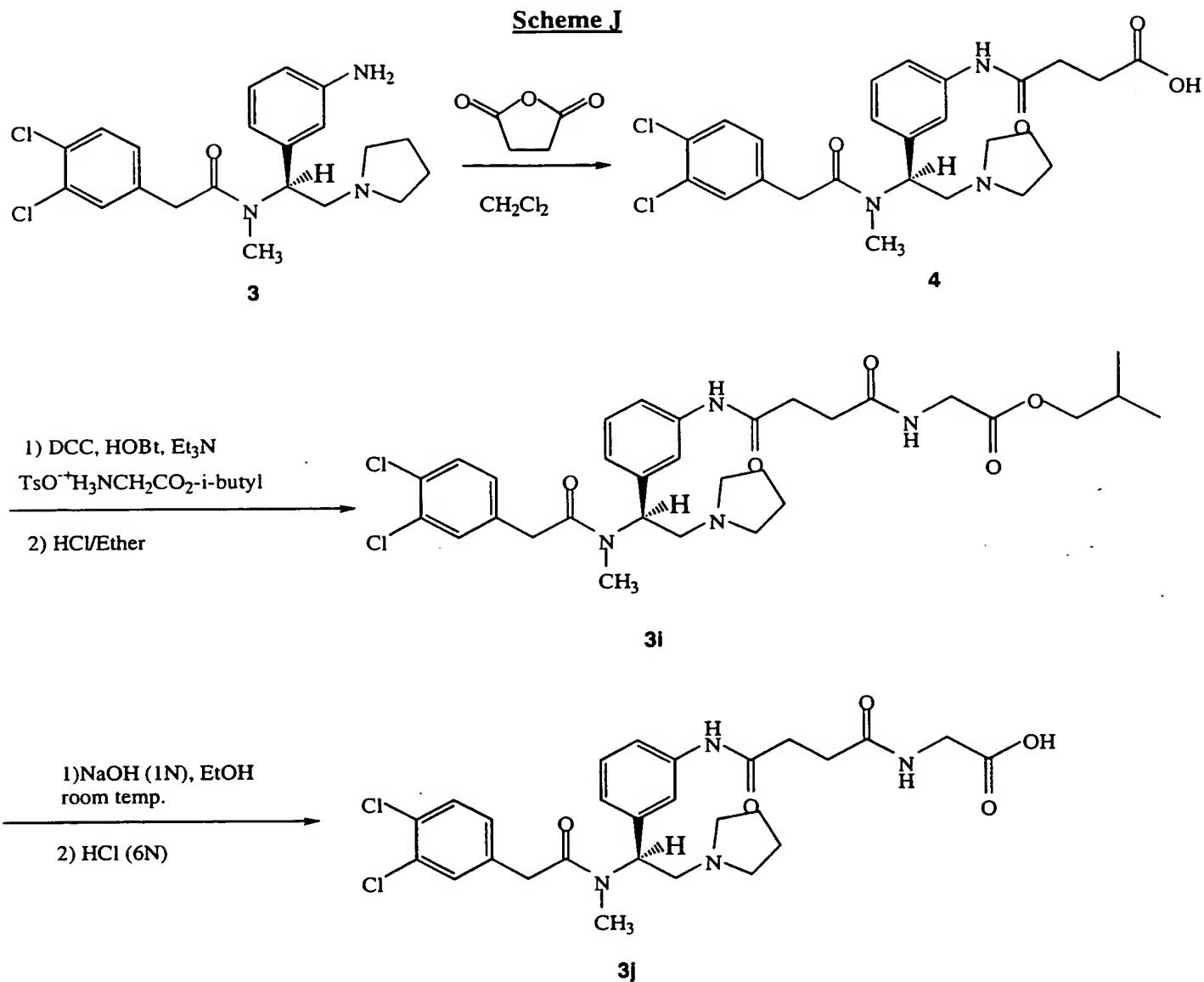


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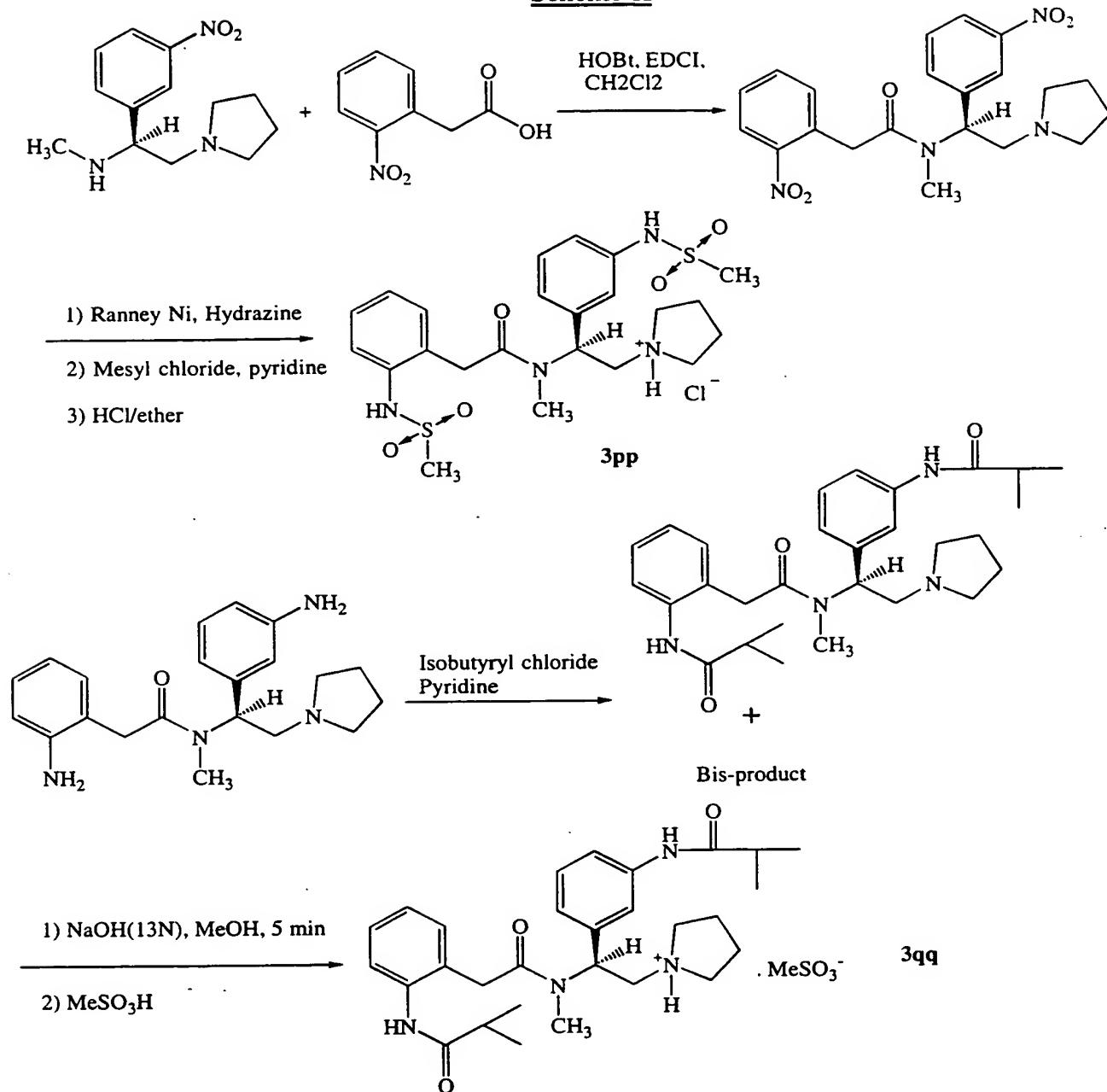
Scheme H

5

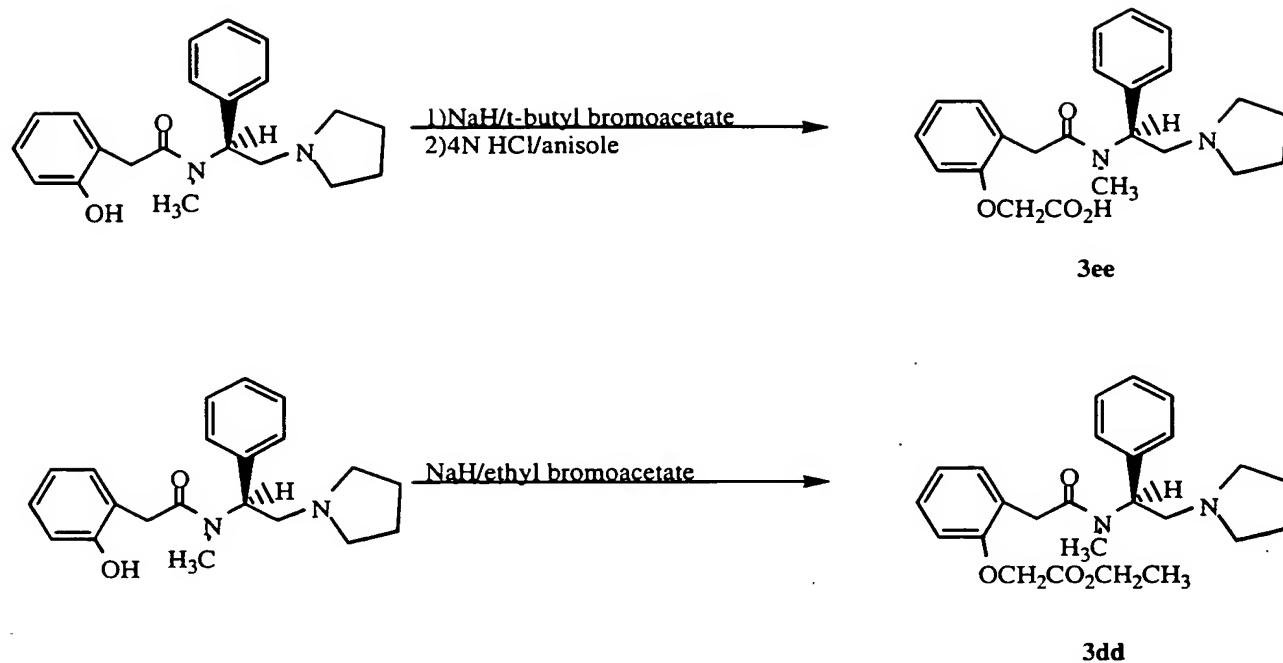
Scheme I

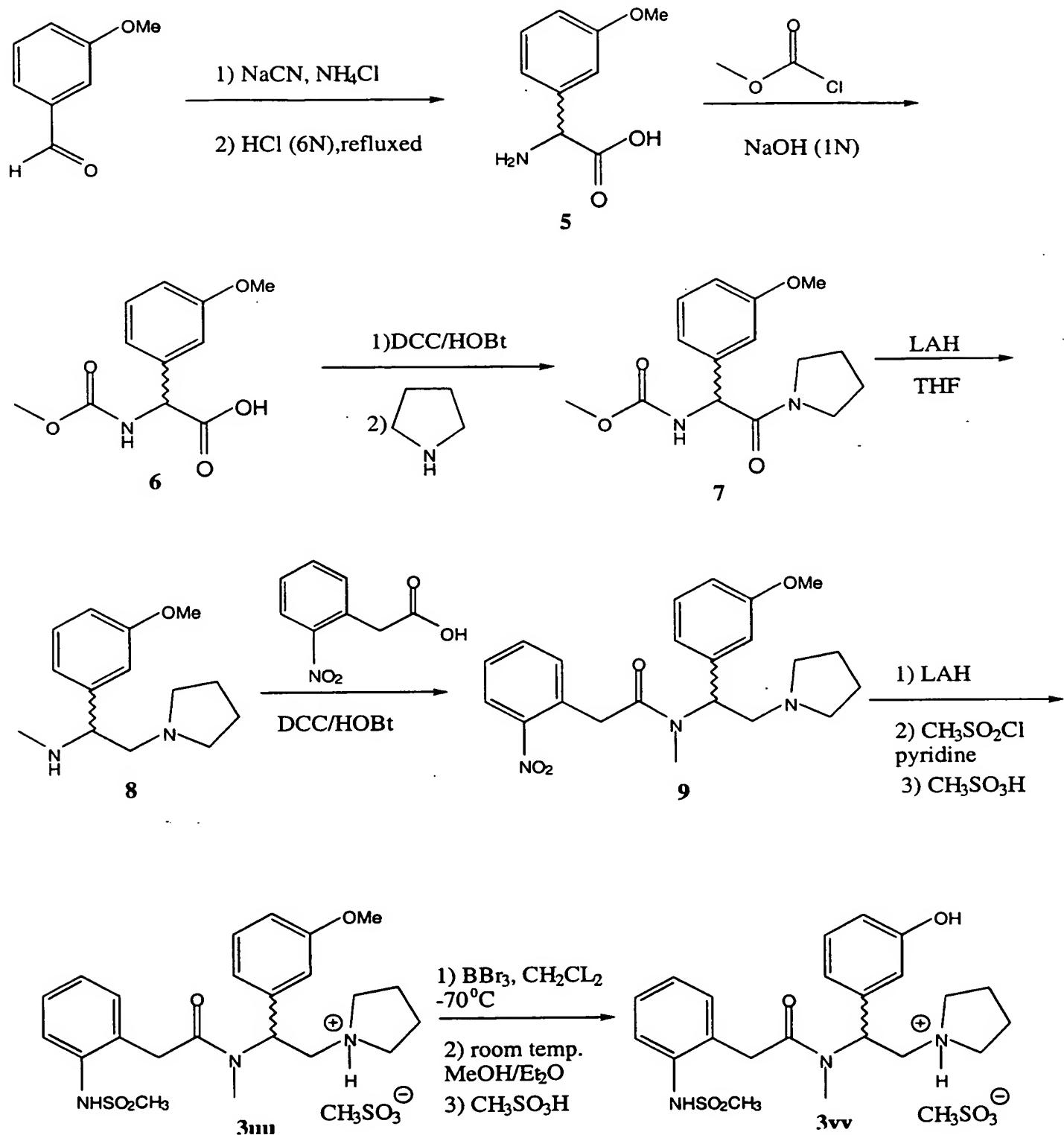
Scheme J

Scheme K

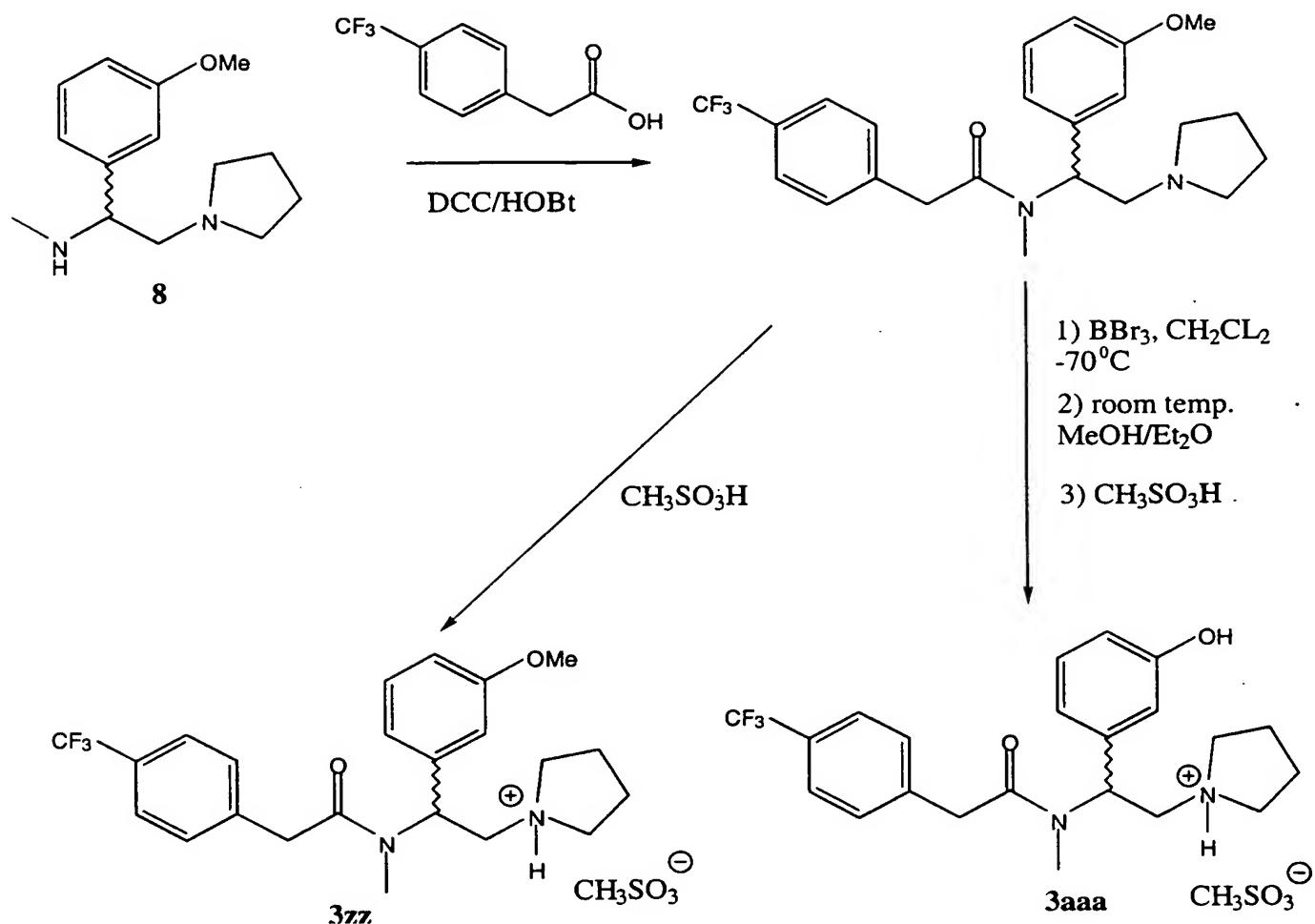


Scheme L



Scheme M

Scheme N



Example 3a2-(2-N-Methylsulfonamido-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

5 2-(N,N-Dimethylsulfonamido-2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-
2-(1-pyrrolidinyl)ethyl]acetamide (for preparation see USP 5,688,955) 130 mg; 0.22 mmol was
treated with 0.2 mL of 10 M NaOH in 3.0 mL of 2:1 MeOH:THF as described in the preparation
of 3rr. The crude product was purified by flash chromatography using a stepwise gradient of 2%
to 4% MeOH:methylene chloride with 2% ammonia to give 100 mg (95%) of desired product
10 which was treated with 1.0 M HCl to afford 3a as a tan solid. Mp 140-142°C; ¹H NMR (HCl salt,
DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.8 (s, 3H, NCH₃), 3.1 (s, 3H, SO₂CH₃), 3.6-3.8 (m, 2H),
4.0-4.3 (q, 2H), 6.0-6.2 (dd, 1H), 7.2-7.6 (complex, 5H, aromatic), 7.7-7.9 (d, 2H), 9.5 (s, NH).
MS(FAB) m/z 483. Anal. (C, H, N) Calcd. for C₂₂H₂₉N₃O₃Cl₂SHCl 0.25 H₂O: C, 50.73; H,
5.42; N, 8.07. Found: C, 49.32; H, 5.52; N, 7.58.

15

Example 3bN-[(4-Trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl)ethyl]acetamido] glycine hydrochloride

20 To a stirred solution of bromoacetic acid (0.75 g, 5.42 mmol) in anhydrous CH₃CN (20
mL) was added N,N-diisopropylethylamine (1.41 g, 11.0 mmol) under a nitrogen atmosphere.
After addition of 2-(2-Amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-
pyrrolidinyl)ethyl]acetamide¹ (2.0 g, 4.93 mmol) in anhydrous CH₃CN (10 mL) to the reaction
mixture, it was heated to 70°C for 6 days. TLC [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH
25 (95:5:2)] of the reaction mixture showed that still some starting material was present. The
reaction mixture was cooled to room temperature and solvent was evaporated to dryness. The
residue was partitioned between CH₂Cl₂ and water, organic layer was separated, dried over
anhydrous Na₂SO₄, and evaporated to dryness to give the crude mixture. The residue was
crystallized from acetone and acetonitrile (1:1) to give the desired compound as a white solid 0.6
30 g which was still contaminated with minor amounts of the starting material.

35 The product 3b was finally purified on Chromatotran (precoated silica plate) using
solvent acetone:water (9:1) and recrystallized from acetonitrile to give the product as a white
solid, 0.35 g (15%); mp 228-230°C (d); MS (FAB) 464 (M+1); ¹H NMR (200 MHz, DMSO-d₆)

δ 2.16 (m, 4H), 2.88 (s, 3H), 3.47-4.00 (m, 9H), 4.50 (m, 1H), 4.95 (m, 1H), 6.34 (d, J = 9.0 Hz, 1H), 6.82 (d, J = 8.0 Hz, 1H), 7.02 (s, 1H), 7.18 (d, J = 7.7 Hz, 1H), 7.55 (m, 5H). Anal. Calcd. for $C_{24}H_{28}F_3N_3O_3 \cdot 0.25H_2O$: C, 61.59; H, 6.14; N, 8.98. Found: C, 61.54; H, 6.10; N, 9.36.

Ref.

5 U. S. Patent, 5,688,955 (1997).

Example 3c

2-(3,4-Dichlorophenyl)-N-methyl-N-[(1R, S)-1-(3-sulfamidophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

10 A solution of compound 1¹ (203 mg, 0.5 mmol) and sulfamide (480 mg, 5 mmol) in dioxane (15 ml) was refluxed for 4 hours in oil bath. After removal of dioxane, the residue was partitioned between NaOH (1N, 50 ml) and $CHCl_3$ (50 ml). The aqueous layer was extracted with $CHCl_3$ (2x25 ml), and the combined extract was washed with brine, dried (Na_2SO_4). Silica column chromatography of crude material gave a pure product that was converted to hydrochloric acid salt with HCl/ether (164 mg, 64%). Mp: 198-200 °C. Spectral data: ¹H NMR (DMSO-d₆) δ 1.97 (m, 4H), 2.80 (s, 3H), 3.12 (m, 2H), 3.52-3.66 (m, 3H), 3.72 (d, J =16.5 Hz, 1H), 4.01-4.10 (m, 2H), 6.04 (d, J =11.0 Hz, 1H), 6.88 (d, J =7.6 Hz, 1H), 6.99 (s, 1H), 7.17 (m, 1H), 7.29 (m, 1H), 7.55 (d, J =4.5 Hz, 1H), 9.10 (s, 1H). Fab MS (MH^+): 485. Anal. Calcd For 20 $C_{21}H_{26}N_4O_3Cl_2S \cdot HCl$: C, 48.33; H, 5.21; N, 10.74. Found: C, 48.31; H, 5.21; N, 10.59.

Example 3d

2-(4-Trifluoromethylphenyl)-N-methyl-N-[(1S)-1-[3-[(methylsulfonyl)amino]phenyl]-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

25 4-Trifluormethylphenyl acetic acid was condensed with (1S)-1-[2-(methylamino)-2-(3-nitrophenyl)-ethyl]pyrrolidine following the methods described in the literature¹ to give the intermediate, 3-nitro-derivative in 95% yield, ¹H NMR (200 MHz, $CDCl_3$) δ 1.68 (m, 4H), 2.35-3.30 (m, 6H), 2.71 (s, 3H), 3.85 (m, 2H), 6.20 (m, 1H), 7.49 (m, 7H), 8.10 (s, 1H). The nitro group was reduced again following the method described in literature (Raney Ni/hydrazine hydrate) to corresponding 3-amino derivative in nearly quantitative yield.

To a solution of the above 3-amino compound (2.9 g, 7.15 mmol) in CH_2Cl_2 (30 mL) was added triethyl amine (3.62 g, 35.76 mmol) and the reaction mixture was cooled to in an ice-bath.

Methane sulfonyl chloride (2.46 g, 21.45 mmol) was added dropwise in 15 min and the ice-bath was removed. The reaction mixture was stirred at room temperature for 72 h. The reaction mixture was quenched with addition of water, organic layer was separated, washed with water, saturated NaHCO_3 , saturated salt solution, and dried over anhydrous Na_2SO_4 . Removal of solvent 5 gave 3-N-(bis-methylsulfonamide) derivative as a foam which was used directly into the following reaction.

The above compound (4.0 g, 7.12 mmol) was dissolved in $\text{CH}_3\text{OH}:\text{THF}$ (2:1, 32 mL) and stirred at room temperature. Sodium hydroxide (10 M aqueous solution) (1.29 g, 32.26 mmol) was added and stirred at room temperature for 20 min [TLC, solvent system: CH_2Cl_2 : CH_3OH : 10 28% NH_4OH (95:5:2)]. Reaction mixture was neutralized with the addition of 1N HCl and evaporated to dryness under reduced pressure. The residue was redissolved in ethyl acetate, washed with saturated NaHCO_3 , saturated salt solution, and dried over anhydrous Na_2SO_4 . Removal of the solvent under reduced pressure gave a yellow foam which was purified on a silica 15 gel column [solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (95:5:2)]. The hydrochloride salt was prepared from 1M ethereal HCl and recrystallized from 2-propano:ether (1:1) to give 3d as a cream colored solid in 45% yield; mp 173-175°C; ^1H NMR (200 MHz, CDCl_3) δ 1.65 (m, 4H), 2.30-3.15 (m, 6H), 2.67 (s, 3H), 2.86 (s, 3H), 3.80 (m, 2H), 6.05 (m, 1H), 7.00-7.25 (m, 4H), 7.35 (d, J = 8.2 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H). Anal. Calcd. for $\text{C}_{23}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_3\text{S} \cdot \text{HCl} \cdot 0.5\text{H}_2\text{O}$: C, 55.22; H, 5.72; N, 7.94. Found: C, 52.17; H, 5.61; N, 7.96.

20

Example 3e

2-(4-Methanesulfonylphenyl)-N-methyl-N-[(1S)-1-[3-[(methylsulfonyl)amino]phenyl]-2-[1-pyrrolidinyl]ethyl}acetamide methanesulfonate

The compound was prepared from 4-methylsulfonylphenyl acetic acid following the 25 procedure described for 3d. The methane sulfonic acid salt was recrystallized from CH_2Cl_2 :ether to give 3e as a beige colored solid in 32% yield; mp 140-142°C; ^1H NMR (300 MHz, DMSO-d_6) δ 2.00 (m, 4H), 2.40 (s, 3H), 2.78 (s, 3H), 2.97 (s, 3H), 3.20 (s, 3H), 3.40-4.10 (m, 6H), 3.94 (d, J = 5.5 Hz, 2H), 6.10 (m, 1H), 7.00 (d, J = 5.8 Hz, 1H), 7.15 (s, 1H), 7.20 (t, J = 6.0 Hz, 1H), 7.35 30 (t, J = 5.5 Hz, 1H), 7.50 (d, J = 12.5 Hz, 2H), 7.85 (d, J = 12.0 Hz, 2H). Anal. Calcd. for $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_5\text{S}_2 \cdot \text{CH}_3\text{SO}_3\text{H} \cdot 2.0\text{H}_2\text{O}$: C, 46.06; H, 6.28; N, 6.71. Found: C, 45.99; H, 6.03; N, 6.55.

Example 3f2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[3-[(methylsulfonyl)amino]phenyl]-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

5 2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[3-(bis-methylsulfonyl)amino]phenyl]-2-[1-pyrrolidinyl]ethyl}acetamide¹ (1.8 g, 3.2 mmol) was dissolved in CH₃OH:THF (2:1, 90 mL) and added 10 M NaOH solution (0.58 g, 14.5 mmol). The reaction was followed by TLC [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (95:5:2)] and worked up as described in case of 3d to give the crude product as a foam. The compound was purified on a silica gel column [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (95:5:2)] and the hydrochloride salt was prepared from 1M etherial HCl. Recrystallization of the salt from CH₂Cl₂:ether (1:1) gave 3f as a beige colored solid, 0.57 g (35%); mp 240-242°C. Anal. Calcd. for C₂₂H₂₇Cl₂N₃O₃S.HCl.0.25H₂O: C, 50.29; H, 5.47; N, 8.00. Found: C, 50.63; H, 5.26; N, 7.66

15

Example 3g2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[3-(diethyl phosphoryl)amino]phenyl]-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

20 2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-[1-pyrrolidinyl]ethyl}-acetamide¹ (0.411 g, 1.011 mmol) was dissolved in anhydrous THF (8 mL) and cooled in an ice-bath under a nitrogen atmosphere. Diisopropylethylamine (1.06 mL, 6.07 mmol) was added followed diethyl chlorophosphate (0.58 mL, 4.045 mmol). The reaction mixture was stirred at room temperature for 48 h, quenched with the addition of water, and evaporated to dryness. The residue was partitioned between CH₂Cl₂ and saturated NaHCO₃ solution. The organic layer was separated, dried over anhydrous sodium sulphate, and evaoparted under reduced pressure to give the crude product. The compound was purified on a silica gel column [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (99:1:2)] and converted to the hydrochloride salt from 1M etherial HCl to give 3g, 0.44 g (81%); mp 140-142°C; ¹H NMR (200 MHz, DMSO-d₆) δ 1.18 (t, J = 8.0 Hz, 3H), 1.95 (m, 4H), 2.77 (s, 3H), 3.00-4.20 (m, 12H), 6.05 (m, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.88 (s, 1H), 7.00 (d, J = 7.5 Hz, 1H), 7.25 (m, 2H), 7.53 (m, 2H), 8.05 (d, J = 8.6 Hz, 1H). Anal. Calcd. for C₂₅H₃₄Cl₂N₃O₄P.HCl.0.5H₂O: C, 51.07; H, 6.17; N, 7.15. Found: C, 50.91; H, 5.93; N, 6.97.

Example 3h**2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[3-[(4-oxo-butenoate)]amino]phenyl]-2-(1-pyrrolidinyl)ethyl]acetamide**

5 2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-(3-aminophenyl)-2-[1-pyrrolidinyl]ethyl]-acetamide¹ (0.0347 g, 0.855 mmol) was dissolved in anhydrous THF (8 mL) under a nitrogen atmosphere and added a solution of maleic anhydride (0.084 g, 0.855 mmol) in anhydrous THF (1 mL) at room temperature. The reaction mixture was stirred at this temperature for 24 h and the resulting solid was filtered, washed with THF and ether. The solid was dried under vacuum to 10 give **3h**, (0.274 g, 63%); mp 174-176°C; MS 504 (m/z); ; ¹H NMR (200 MHz, DMSO-d₆) δ 1.79 (m, 4H), 2.72(s, 3H), 2.85-3.85 (m, 6H), 5.95 (m, 1H), 6.10 (m, 1H), 6.25 (m, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.28 (m, 2H), 7.55 (m, 4H). Anal. Calcd. for C₂₅H₂₇Cl₂N₃O₄·0.25H₂O: C, 59.00; H, 5.45; N, 8.26. Found: C, 58.69; H, 5.18; N, 8.01.

15

Example 3i**2-(3,4-Dichlorophenyl)-N-methyl-N-[(1S)-1-[3-[(3-((iso-butoxycarbonyl)-methyl)aminocarbonyl)propionamido]phenyl]-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride**

20 A solution of compound **1** (222 mg, 0.546 mmol) in CH₂Cl₂ (10 ml) at 0 °C was treated with succinic anhydride (82 mg, 0.819 mmol). The mixture was allowed to warm up to room temperature and stirred for 18 hours. The solvent was removed by rotary evaporation and the residue was recrystallized from ethyl acetate and hexane (249 mg, 89%).

25 A mixture of the above compound (246 mg, 0.486 mmol), 1-hydroxybenzotriazole monohydrate (98 mg, 0.729 mmol), and p-toluenesulfonic acid salt of 2-methylpropyl glycine (221 mg, 0.729 mmol) in THF (5 ml) was treated with Et₃N (0.102 ml, 0.729 mmol), followed by dicyclohexylcarbodiimide (150 mg, 0.729 mmol) in THF (2 ml). The mixture was stirred at room temperature for 48 hours, cooled in ice bath, and filtered. The filtrate was concentrated, dissolved in ethyl acetate, and the solution was washed with aqueous NaHCO₃ (saturated), water, 30 brine, dried (Na₂SO₄). After concentration, the residue was allowed to pass through a silica column eluted with 2% MeOH in CH₂Cl₂ (2% ammonia). 216 mg of the desired product was obtained (72%) and part of the product was converted to the hydrochloric acid salt (compound **3i**, 67 mg). Mp: 85 °C (decomposed). Spectral data: ¹H NMR (DMSO-d₆) δ 0.86 (d, J=6.7 Hz, 6H), 1.84 (m, 1H), 1.97 (m, 4H), 2.40-2.50 (m, 4H), 2.77 (s, 3H), 3.14 (m, 1H), 3.47-3.70 (m,

3H), 3.75-3.83 (m, 5H), 3.98-4.14 (m, 2H), 6.06 (d, $J=10.0$ Hz, 1H), 6.93 (d, $J=7.7$ Hz, 1H), 7.30 (m, 2H), 7.50-7.57 (m, 4H), 8.37 (bs, 1H). Fab MS (MH^+): 485. Anal. Calcd for $C_{31}H_{40}N_4O_5C_{12}HCl.1.2H_2O$: C, 54.94; H, 6.46; N, 8.27. Found: C, 54.94; H, 6.43; N, 8.28.

5

Example 3j2-(3,4-Dichlorophenyl)-N-methyl-N-[(1R, S)-1-[3-(3-((hydroxycarbonyl)-methyl)aminocarbonyl)propionamido)phenyl]-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

10 A solution of compound 3i (144 mg, 0.233 mmol) in ethanol (3 ml) and water (1 ml) was cooled in ice bath and treated with NaOH (1N, 0.7 ml) slowly. After stirring at room temperature for 1 hour, the solution was adjusted to pH = 5 with 6N HCl. The mixture was stirred for 2 hours and then concentrated. The residue was separated by reversed phase TLC plate to give the final product (114 mg, 80%). Mp: 158 0C (decomposed). Spectral data: 1H NMR (DMSO- d_6) δ 1.65 (bs, 4H), 2.40-2.64 (m, 4H), 2.70 (s, 3H), 3.11 (m, 2H), 3.33 (m, 2H), 3.71 (m, 3H), 3.86 (d, $J=16.0$ Hz, 1H), 5.81 (dd, $J=9.9, 4.9$ Hz, 1H), 6.94 (d, $J=8.1$ Hz, 1H), 7.23 (t, $J=7.8$ Hz, 1H), 7.48-7.56 (m, 4H), 8.17 (bs, 1H), 9.95 (s, 1H). Fab MS (MH^+): 563. Anal. Calcd for $C_{27}H_{32}N_4O_5Cl_2HCl.0.75H_2O$: C, 52.79; H, 5.68; N, 9.12. Found: C, 52.83; H, 5.92; N, 9.10.

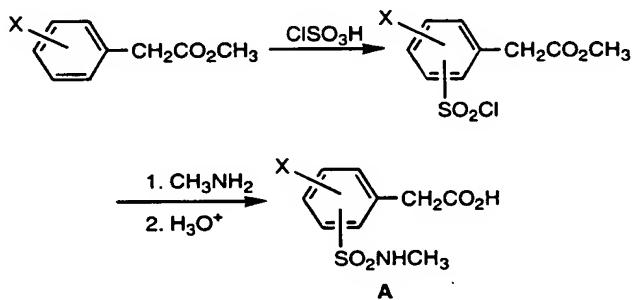
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Example 3k2-[(2-N-Phenylsulfonamido)-phenyl]-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide methane sulfonate

25 2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (for preparation see USP 5,688,955) 1.2 g (3.55 mmol) was stirred in 30mL of dry CH_2Cl_2 at 0^0C . Triethylamine (0.5 mL; 3.55 mmol) and benzenesulfonyl chloride (0.45 mL; 3.55 mmol) in 10 mL of dry CH_2Cl_2 were added. After the addition the reaction solution was allowed to warm to room temperature and stirred overnight. TLC (90:10 methylene chloride : methanol w/2% ammonia) indicated the reaction was incomplete. 0.22 mL (1.7 mmol) of the chloride and 0.25 mL (1.7 mmol) of the base were added at 0^0C . The solution was stirred for 24 h at room temperature before it was complete. The reaction was quenched with sat. sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo* to give 1.9 g of crude product which was purified by flash chromatography using a stepwise gradient of 2% to 7% MeOH: methylene chloride w /2% ammonia to yield 1.2 g

of bis-alkylated product which was hydrolyzed using the same preparation as 3rr to afford 900 mg (53%) of desired product which was treated with 1.0 eq. of methanesulfonic acid to give 3k as a tan solid. mp 205-207°C; ¹H NMR (mesylate salt, CDCl₃) δ 1.8(br m, 1H), 2.1(br d, 2H), 2.2(br t, 2H), 2.8(s, 3H, NCH₃), 3.1(t, 1H), 4.0-4.3(d, 2H), 6.2(dd, 1H), 7.0(d, 2H), 7.1(m, 2H), 5 7.30 (complex, 5H, aromatic), 7.4(d, 1H), 7.5(d, 1H), 7.9(d, 2H), 9.0(s, 1H), 10.3(br, NH). MS(FAB) m/z 477. Anal. (C₂H₃₁N₃O₃S CH₃SO₃H: C, 58.62; H, 6.15; N, 7.32. Found: C, 58.66; H, 6.20; N, 7.27.

10 General procedure for the preparation of N-methyl sulfamoyl derivatives of phenyl acetic acids



15 To a stirred ice-cold chlorosulfonic acid (43.82 g, 0.376 mol) under anhydrous condition was added dropwise methyl phenylacetate (6.23 g, 0.042 mol). When addition was completed, the reaction mixture was then stirred at room temperature and the progress of the reaction was monitored by TLC [solvent: hexane :ethyl acetate (4:1)] [In this case the reaction was over in 30 min and however depending upon the substitution (X = H) of the aromatic ring, reaction may take 20 from 12 to 72 h at room temperature]. Reaction mixture was then carefully poured on ice-water and the product was extracted with ether several times. The combined etherial solution was washed with water, saturated salt solution, and dried over anhydrous sodium sulfate. Removal of ether under reduced pressure resulted in a mixture of 2- and 4-chlorosulfonyl compounds (63-85% yields) (chlorosulfonation was also depended upon the directing effects of the X group) 25 which were used directly into next reaction.

To a stirred solution of methyl amine (19.5 ml, 2 M in THF, 0.039 mol) at 0°C under a nitrogen atmosphere was added a solution of above chlorosulfonyl derivative (3.25 g, 0.013 mo)

in anhydrous THF (10 mL). Reaction mixture was stirred 15 min at this temperature and 1-4 h at room temperature by this time TLC [solvent: hexane :ethyl acetate (4:1)] showed no starting material was present. The solvent was removed under reduced pressure and the residue was partitioned between ethyl acetate and water. The organic layer was separated washed with 5 saturated salt solution, dried over anhydrous sodium sulfate, and evaporated to dryness to give methyl sulfonamide derivative (90-96% yield). In most cases this product was pure enough to proceed to next step, otherwise purified on a silica gel column before the hydrolysis of the ester.

The methyl sulfonamide ester (3.0 g, 12.34 mmol) was suspended in 3N aqueous HCl and heated to reflux with stirring for 24 h. The solvent was removed under reduced pressure and the 10 residue was re-dissolved in CH_2Cl_2 , filtered, and concentrated to a small volume. Addition of either ether or hexane gave compound A in 80-95% yield and these acids were used in the condensation reactions.

Example 3l

15 2-[3-(N-Methylsulfamoyl)-4-chlorophenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

To a solution of 3-(N-methylsulfamoyl)-4-chlorophenyl acetic acid (prepared from 4-chlorophenyl acetic acid, 1.58 g, 6.0 mmol) in anhydrous CH_2Cl_2 (20 mL) under a nitrogen 20 atmosphere was add N-hydroxybezotriazole (0.81 g, 6.0 mmol). Reaction mixture was stirred at room temperature for 15 min then cooled in an ice-bath and added 1-(3-diethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.165 g, 6.0 mmol). Stirring was continued at ice-bath temperature for 30 min then added a solution of (1S)-1-[(2-methylamino-2-phenyl)ethyl]pyrrolidine¹ (1.02 g, 5.0 mmol) in anhydrous CH_2Cl_2 (10 mL) followed by N,N-diisopropylethylamine (0.79 g, 6.1 mmol). Reaction mixture was continued stirring for 48 h [TLC, solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (95:5:2)]. After addition of more CH_2Cl_2 , the organic phase was washed with water, saturated sodium bicarbonate solution, saturated salt 25 solution, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude product which was converted to the hydrochloride salt from 1M ethereal diisopropylethylamine (0.79 g, 6.1 mmol). Reaction mixture was continued stirring for 48 h [TLC, solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (95:5:2)]. After addition of more CH_2Cl_2 , the organic phase was washed with water, saturated sodium bicarbonate solution, saturated salt 30 solution, and dried over anhydrous sodium sulfate. Removal of the solvent under reduced pressure gave the crude product which was converted to the hydrochloride salt from 1M ethereal HCl. The salt was re-crystallized from 2-propanol to give 3l as off-white solid, 1.52 g (62%); 285-287°C; ¹H NMR (300 MHz, DMSO-d₆) δ 2.01 (m, 4H), 2.50 (d, J = 4.5 Hz, 3H), 2.87 (s, 3H), 3.17 (m, 2H), 3.64 (m, 3H), 3.90 (d, J = 10.0 Hz, 1H), 4.14 (d, J = 10.5 Hz, 2H), 6.20 (m,

1H), 7.28-7.45 (m, 4H), 7.55-7.65 (m, 3H), 7.90 (d, J = 3.5 Hz, 1H). Anal. Calcd. for $C_{22}H_{28}ClN_3O_3S \cdot HCl \cdot 0.75H_2O$: C, 52.85; H, 6.15; N, 8.40. Found: C, 52.84; H, 5.89; N, 8.40.

Example 3m

2-(3-Sulfamoyl-4-chlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl]ethyl]acetamide methanesulfonate

Prepared from 3-sulfonamido-4-chlorophenyl acetic acid following the above procedure and the free base was converted to methanesulfonic acid salt. Recrystallization from 2-propanol gave **3m** as a white solid in 51% yield; mp 220-222°C; MS (FAB) 436 (M+1); ¹H NMR (300 MHz, DMSO-d₆) δ 2.00 (m, 4H), 2.36 (s, 3H), 2.76 (s, 3H), 3.20 (m, 2H), 3.50-3.80 (m, 4H), 3.94 (bs, 2H), 6.15 (m, 1H), 7.25 (d, J = 6.0 Hz, 1H), 7.30-7.65 (m, 6H), 7.88 (d, J = 2.5 Hz, 1H). Anal. Calcd. for C₂₁H₂₆ClN₃O₃S.CH₃SO₃H: C, 49.66; H, 5.68; N, 7.90. Found: C, 49.69; H, 5.63; N, 7.78.

Example 3n

2-(3-Sulfamoyl-4-chlorophenyl)-N-methyl-N-[(1*S*)-1-[3-[(methylsulfonyl)amino]phenyl]-2-[1-pyrrolidinyl]ethyl]acetamide methanesulfonate

20 (S)-1-[2-(Methylamino)-2-(3-nitrophenyl)ethyl]pyrrolidine¹ was condensed with 3-sulfonamido-4-chlorophenyl acetic acid following the general procedure described in 83% yield. The catalytic reduction of the 3-nitro group was done with PtO₂ to give the 3-amino intermediate. Bis-mesylation of the 3-amino group followed by selective removal one of the mesyl group as described for **3d** resulted in the desired compound in 28% yield. Methanesulfonic acid salt was prepared in 71% yield to give **3n**; mp 170-173°C; MS (FAB) 543 (M+1); ¹H NMR (300 MHz, DMSO-d₆) δ 1.98 (m, 4H), 2.35 (s, 3H), 2.44 (d, J = 5.0 Hz, 3H), 2.77 (s, 3H), 2.98 (s, 3H), 3.10-4.15 (m, 6H), 3.90 (d, J = 8.0 Hz, 2H), 6.20 (m, 1H), 7.00-7.75 (m, 6H), 7.90 (d, J = 2.0 Hz, 1H). Anal. Calcd. for C₂₃H₃₁ClN₄O₅S₂·CH₃SO₃H·0.5H₂O: C, 44.47; H, 5.60; N, 8.64. Found: C, 44.26; H, 5.53; N, 8.45.

Example 3o2-[3-(N-Methylsulfamoyl)-4-fluorophenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

5 Prepared from 3-methylsulfonamido-4-fluorophenyl acetic acid following the above procedure to give **3o** as a white solid in 85% yield; mp 278-280°C; ¹H NMR (free base, 200 MHz, CDCl₃) δ 1.73 (m, 4H), 2.61 (bs, 3H), 2.68 (s, 3H), 2.90-3.20 (m, 2H), 3.55-3.90 (m, 3H), 4.75 (b, 1H), 6.05 (m, 1H), 7.05-7.60 (m, 7H), 7.72 (bd, 1H). Anal. Calcd. for C₂₂H₂₈FN₃O₃S.HCl: C, 56.22; H, 6.22; N, 8.94. Found: C, 56.22; H, 6.24; N, 8.86.

10

Example 3p and 3r2-[2&4-(N-Methylsulfamoyl)-phenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

15 Compounds **3p** and **3r** were prepared using the general EDCI/DIPEA coupling procedure of (1S)-N-methyl-2-pyrrolidino-1-phenethylamine (1.3 g; 6.34 mmol), a mixture of 2 and 4 substituted reversed sulfamides acids (1.6 g; 6.98 mmol), HOBT (943 mg; 6.9 mmol), EDCI (1.33 g; 6.98 mmol) and DIPEA (1.32 mL; 7.60 mmol). After 24 hours, TLC (95:5 methylene chloride: methanol with 2% ammonia) indicates the reaction is complete. After the standard 20 work-up, the crude product was purified using a stepwise gradient of 2% to 10% MeOH: methylene chloride with 2% ammonia to afford 1.6 g of a mixture of the 2 and 4 substituted sulfamide products. The mixture was separated using a stepwise gradient of 1% to 2% MeOH: methylene chloride with 2% ammonia on a chromatotran to afford 14 mg (0.5%) of the 2-substituted compound **3p** and 20 mg (0.7%) of the 4-substituted compound **3r**, which were 25 converted to the HCl salt with 1.0 M HCl in diethyl ether. ¹H NMR (HCl salt, CDCl₃) δ 1.7(br s, 4H, -CH₂CH₂-), 2.4-2.6(m, 2H), 2.6(d, 3H, NHCH₃), 2.8(s, 3H, NCH₃), 3.0-3.3(t, 2H), 3.8(d, 2H), 6.0-6.2(dd, 1H), 7.2-7.4(complex, 5H, aromatic), 7.5-7.7(m, 2H), 7.8(s, 2H). MS(FAB) m/z 415.

30

Example 3q3-(N-Methylsulfamoyl)-phenyl-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

5 Compound **3q** was prepared using the HOBT/EDCI coupling procedure described in USP 5,885,955 with 3-SO₂NHCH₃ phenyl acetic acid (A) 2.23 g; 9.73 mmol, (1S)-N-methyl-2-pyrrolidino-1-phenethylamine(1.90 g; 9.26 mmol), HOBT (1.31 g; 9.73 mmol), EDCI (1.85 g; 9.73 mmol) and DIPEA (3.38 mL; 19.46 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 8% MeOH: methylene chloride with 2% ammonia to give 1.40 g (40%) of desired product which was treated with 1.0 M HCl in diethyl ether to afford **3q** as the HCl salt. mp >250°C(dec.); ¹H NMR (HCl salt, CDCl₃ with 3 drops of CD₃OD) δ 2.0-2.2(br, 4H, -CH₂CH₂-), 2.6(s, 3H, NHCH₃), 2.8(s, 3H, NCH₃), 3.4-3.5(d, 2H), 6.3-6.4(dd, 1H), 7.2(d, 2H), 7.3-7.4(complex, 5H, aromatic), 7.5(t, 1H), 7.6(d, 1H), 7.7(d, 1H), 7.8(s, 1H). MS(FAB) m/z 415. Anal. (C,H,N) Calcd. for C₂₂H₂₉N₃O₃S·HCl: C, 58.46; H, 6.69; N, 9.30. Found C, 59.34; H, 6.62; N, 9.19.

Example 3s2-[N-Methylsulfamoyl]-4-bromo-phenyl-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl]ethyl]acetamide hydrochloride

20 Compound **3s** was prepared using the HOBT/EDCI coupling procedure described in USP 5,885,955 using 2-SO₂NHCH₃, 4-bromophenyl acetic acid (2.3 g; 7.40 mmol), (1S)-N-methyl-2-pyrrolidino-1-phenethylamine (1.4 g; 7.08 mmol), HOBT (1.0 g; 7.46 mmol), EDCI (1.4 g; 7.46 mmol)and DIPEA (1.5 mL; 8.95 mmol). The crude product was purified by flash chromatography using a stepwise gradient of 2% to 8% MeOH: methylene chloride with 2% ammonia to give 500 mg (30%) of **3s** as the desired product which was treated with 1.0 M HCl in diethyl ether to afford the HCl salt. mp >280°C; MS(FAB) m/z 494. Anal. (C,H,N) Calcd. for C₂₂H₂₈N₃O₃S Br·HCl·0.5 H₂O: C, 49.77; H, 5.51; N, 7.91. Found: C, 48.86; H, 5.36; N, 7.67.

Ref.

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Example 3w(Z)-4-[2-(2-Amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl]-2-[1-pyrrolidinyl]ethyl]acetamido]4-oxo-butanoic acid

To a solution of 2-(2-Amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)-ethyl]acetamide¹ (0.86 g, 2.0 mmol) in anhydrous THF under a nitrogen atmosphere 5 was added succinic anhydride (0.25 g, 2.5 mmol). The reaction mixture was stirred at room 10 temperature for 96 h and added excess of anhydrous ether. The resulting solid was filtered off, washed with ether and dried to give crude product. The compound was purified on a silica gel column (acetone:water, 9:1). The desired compound was re-dissolved in CH₂Cl₂, filtered, and 15 concentrated to a small volume. Addition of ether resulted the solid which was filtered, washed with ether, and dried to give 3w (0.32 g, 30%); mp 168-170°C; ¹H NMR (300 MHz, CDCl₃) δ 2.03 (m, 4H), 2.36 (m, 1H), 2.66 (m, 2H), 2.81 (s, 3H), 2.80-2.95 (m, 2H), 3.10 (m, 1H), 3.40 (d, J = 14.0 Hz, 1H), 3.67 (d, J = 14.5 Hz, 1H), 4.18 (t, J = 12.0 Hz, 1H), 6.40 (d, J = 11.5 Hz, 1H), 7.20 (m, 3H), 7.45 (m, 3H), 8.00 (s, 1H). Anal. Calcd. for C₂₅H₂₉Cl₂N₃O₄S₂·0.5H₂O: C, 58.26; H, 5.87; N, 8.15. Found: C, 58.08; H, 5.75; N, 7.96.

20

Example 3x(Z)-4-[2-(2-Amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl]-2-[1-pyrrolidinyl]-ethyl]acetamido]4-oxo-2-butenoic acid

To a solution of 2-(2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)-ethyl]acetamide¹ (0.8 g, 1.85 mmol) in anhydrous THF (10 mL) under a nitrogen atmosphere was added maleic anhydride (0.181 g, 1.85 mmol) and the stirred at room 25 temperature for 4 days. After addition of anhydrous ether, the resulting solid was sonicated and filtered. Recrystallization of the solid from CH₂Cl₂:ether (1:1) gave 3x (0.51 g, 52% yield); mp 158-160°C (d); ¹H NMR (200, MHz, CDCl₃) δ 2.00 (m, 4H), 2.72 (s, 3H), 2.75-3.20 (m, 2H), 3.35 (d, J = 12.5 Hz, 1H), 3.85 (d, J = 13.0 Hz, 1H), 3.90-4.20 (m, 2H), 6.10 (d, J = 12.5 Hz, 1H), 6.25 (m, 2H), 7.15 (m, 3H), 7.44 (m, 3H), 8.00 (s, 1H). Anal. Calcd. for 30 C₂₅H₂₇Cl₂N₃O₄·0.25H₂O: C, 59.00; H, 5.45; N, 8.26. Found: C, 59.20; H, 5.57; N, 7.90.

Example 3y(E) Ethyl 4-[2-(2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl]-2-[1-pyrrolidinyl]ethyl]acetamido]4-oxo-2-butenoate hydrochloride

5 To a solution of fumaric acid monoethyl ester (1.30 g, 9.02 mmol) in anhydrous CH_2Cl_2 (20 mL) under an nitrogen atmosphere was added DCC (1.86 g, 9.03 mmol) followed by pyridine (0.43 mL, 5.31 mmol). The reaction mixture was stirred at room temperature for 30 min then added a solution of 2-(2-amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl]-2-(1-pyrrolidinyl)-ethyl]acetamide¹ (2.30 g, 5.31 mmol) in anhydrous CH_2Cl_2 (10 mL). The reaction 10 mixture was stirred at this temperature for 72 h, filtered and evaporated to dryness to give the crude product. The compound was purified on asilica gel column [solvent system: CH_2Cl_2 :
CH₃OH: 28% NH₄OH (99:1:2)] to give the free base of the desired product. The hydrochloride salt was prepared from 1M etherial HCl and recrystallized from CH_2Cl_2 :ether (1:1) to give 3y (2.0 g, 60%); mp 165-167°C (d); ¹H NMR (300, MHz, CDCl_3) δ 1.28 (t, *J* = 7.0 Hz, 3H), 2.00-2.40 (m, 4H), 2.89 (s, 3H), 2.96 (m, 2H), 3.28 (m, 1H), 3.50 (m, 2H), 3.95-4.10 (m, 4H), 4.21 (q, *J* = 7.1 Hz, 2H), 4.50 (d, *J* = 15.0 Hz, 1H), 6.33 (d, *J* = 10.0 Hz, 1H), 6.89 (d, *J* = 15.0 Hz, 1H), 15 7.10-7.40 (m, 5H), 7.93 (d, *J* = 15.3 Hz, 1H), 8.43 (s, 1H) . Anal. Calcd. for C₂₇H₃₁Cl₂N₃O₄.HCl.H₂O: C, 55.25; H, 5.84; N, 7.16. Found: C, 55.63; H, 5.73; N, 6.94.

Example 3z(Z)-4-[2-(2-Amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl]-2-[1-pyrrolidinyl]-ethyl]acetamido]4-oxo-2-butenoic acid

20 The compound 3z was prepared from 2-(2-amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl]-2-(1-pyrrolidinyl)-ethyl]acetamide¹ following the above in 40% yield; mp 153-155°C (d); MS (FAB) 504 (M+1); ¹H NMR (200, MHz, DMSO-d₆) δ 2.01 (m, 4H), 2.85 (s, 3H), 25 2.85-3.30 (m, 2H), 3.40 (d, *J* = 14.5 Hz, 1H), 3.95 (d, *J* = 14.0 Hz, 1H), 4.10 (m, 2H), 6.30 (m, 3H), 7.18 (m, 3H), 7.38 (m, 4H), 8.15 (s, 1H) . Anal. Calcd. for C₂₆H₂₈F₃N₃O₄.0.75H₂O: C, 60.40; H, 5.75; N, 8.13. Found: C, 60.07; H, 5.50; N, 7.91.

Example 3aa(Z)-4-[2-(2-Aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)-ethyl]acetamido]4-oxo-2-butenoic acid hemimaleate

5 The compound **3aa** was prepared from 2-(2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)-ethyl]acetamide¹ following the above in 93% yield; mp 149-151°C; Anal. Calcd. for C₂₅H₂₉N₃O₄·0.5C₄H₄O₄·H₂O: C, 63.39; H, 6.50; N, 8.21. Found: C, 63.37; H, 6.20; N, 8.22.

Example 3bb2-(N,N-Bisacetic acid-2-amino- α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

10 2-(2-Amino, α,α,α -trifluoro-4-tolyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (for the preparation see USP 5,688,955) 2.0 g; 4.93 mmol was dissolved in 50 ml of dry THF at 0°C. DIPEA (5.15 mL; 29.6 mmol) and t-butyl bromoacetate (3.64 mL; 24.65 mmol) were added 15 minutes apart. The reaction was allowed to warm to room temperature and stirred for 4 days. TLC (95:5 methylene chloride: methanol with 2% ammonia) indicated the reaction is incomplete. Added 1.67 mL (9.58 mmol) of DIPEA to the reaction. After 24 hours the reaction mixture was concentrated to a residue. The residue was dissolved in methylene chloride and washed with sat. sodium bicarbonate and brine. The organic layer was dried (anh. Na₂SO₄), filtered and concentrated *in vacuo* to give a yellow oil. The crude product was purified by flash chromatography using a stepwise gradient of 1% to 8% MeOH: methylene chloride with 2% ammonia to afford 1.2g (61%) of bis-alkylated material which was used in the next step [¹H NMR, (Free base, CDCl₃) δ 1.4 (s, 9H, t-butyl), 1.5(s, 9H, t-butyl), 1.7-1.9(m, 4H), 3.2(s, 3H, NCH₃), 3.6-3.7(dd, 4H), 4.3-4.8(q, 4H), 5.7-5.9(dd, 1H), 6.0(d, 1H), 6.4(d, 1H), 6.6(s, 1H), 6.9-25 7.2(m, 2H), 7.4(complex, 3H, aromatic). MS(FAB) m/z 633. The bis-alkylated compound (1.2 g; 1.89 mmol) was stirred in 33 mL of glacial acetic acid with 4 drops of anisole. After 60 hours, the reaction was concentrated *in vacuo*. The residue was dissolved in acetonitrile and added drop-wise to a solution of 1.0 M HCl in diethyl ether. The precipitate was collected by filtration and dried at 40°C under vacuum to yield 960 mg (93%) of **3bb** as a tan solid. mp 166-169°C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.6(br s, 4H, -CH₂CH₂-), 2.9(s, 3H, NCH₃), 3.8(q, 4H), 4.1-4.3(d, 2H), 4.7-4.9(m, 3H), 6.6(br d, 1H), 7.1(s, 1H), 7.4(d, 1H), 7.6(d, 1H), 7.7-8.0(complex, 5H, aromatic). MS(FAB) m/z 521. Anal. (C,H,N) Calcd. for C₂₆H₃₀N₅O₃F₃·2 HCl ·H₂O: C, 58.46; H, 6.69; N, 9.30. Found: C, 58.40; H, 6.65; N, 9.21.

Example 3cc3-[2-N-Methylsulfonamido-phenyl]-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

5 Compound 3cc was prepared using the same procedure as described in the preparation of compound (2-N-Methylsulfonyl-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (for the preparation see USP 5,688,955). Compound 3-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (1.0 g; 2.02 mmol), 10 mL of 10 M NaOH and 30 mL of 2:1 MeOH: THF. The crude 10 product was clean by TLC and ¹H NMR (760 mg; 90%). The product was treated with 1.0 M HCl in diethyl ether to give 3cc as the HCl salt; mp 155-160°C(dec.); ¹H NMR (Free base, CDCl₃) δ 1.7(br s, 4H, -CH₂CH₂-), 2.5(br d, 2H), 2.8(s, 3H, NCH₃), 2.9(s, 3H, SO₂CH₃), 3.7(d, 2H), 6.0-6.1(dd, 1H), 7.0-7.4(complex, 9H, aromatic). MS(FAB) m/z 415. Anal. (C,H,N) Calc. for C₂₂H₂₉N₃O₃S · HCl: C, 58.46; H, 6.69; N, 9.30. Found: C, 58.40; H, 6.65; N, 9.21.

15

Example 3dd2-(O-Butylacetate)-phenyl-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl]ethyl acetamide hydrochloride

20 2-(2-Hydroxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (for preparation see USP 5,688,955,) 1.3 g;(3.80 mmol) was dissolved in 10mL of dry THF and added to a 0°C slurry of NaH (95%, 100 mg; 4.03 mmol) in dry THF. The mixture was allowed to warm to room temperature for 30 minutes, then cooled to 0°C . Ethyl bromoacetate (0.44 mL; 4.03 mmol) was added drop-wise over a few minutes. After 30 minutes, the mixture was warmed to 25 room temperature and stirred for 5 days. TLC(95:5 methylene chloride: methanol with 2% ammonia) indicated the reaction was complete. The reaction was quenched with sat. ammonium chloride and concentrated *in vacuo*. The residue was dissolved in methylene chloride and separated from water. The organic layer was washed with brine, dried (anh. Na₂SO₄), filtered and concentrated *in vacuo* to give 1.61 g of crude product, which was purified by flash chromatography using a stepwise gradient of 2% to 9% MeOH: methylene chloride with 2% ammonia to afford 1.0 g (70%) of 3dd as a desired product, which was treated with 1.0 M HCl in diethyl ether to give the HCl salt. mp 184-187°C; ¹H NMR (HCl salt, CDCl₃) δ 1.2 (t, 3H), 1.7-1.9 (br s, 4H, -CH₂CH₂-), 2.0 (br d, 2H), 2.2-2.5 (m, 2H), 2.8-3.0(m, 2H), 3.0 (s, 3H, NCH₃), 3.3-3.5 (t, 1H), 4.0-4.1 (m, 2H), 4.2 (q, 2H), 6.2-6.3 (dd, 1H), 6.8 (d, 1H), 6.9-7.1 (t, 1H), 7.2-7.5

(complex, 7H, aromatic). MS(FAB) m/z 424. Anal. (C,H,N) Calcd. for C₂₅H₃₂N₂O₄·HCl·0.5 H₂O: C, 65.14; H, 7.22; N, 6.08. Found: C, 63.70; H, 7.00; N, 6.09.

Example 3ee

2-[Phenoxy-acetyl]methylamino-(1-pyrrolidinyl) ethyl]acetamide]hydrochloride

2-(2-Hydroxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (for the preparation see USP 5,688,955) 960 mg; 2.83 mmol was dissolved in 6.0 mL of dry THF and added to a slurry of NaH (95%) 79 mg; 3.12 mmol in dry THF at 0°C. The mixture was allowed 10 to warm to room temperature and stirred for 30 minutes, then cooled to 0°C when t-butyl bromoacetate (0.42 ml; 2.83 mmol) in 2 mL of dry THF was added drop-wise. The solution was allowed to warm to room temperature and stirred overnight. TLC (95:5 methylene chloride: methanol w/ 2% ammonia) indicated the reaction was complete. The reaction was quenched with saturated ammonium chloride and concentrated *in vacuo*. The residue was dissolved in methylene 15 chloride and separated from water. The organic layer was washed with brine, dried (anh. Na₂SO₄), filtered, and evaporated to give a brown residue. The crude product was purified by flash chromatography using a stepwise gradient of 1% to 8% MeOH: methylene chloride with 2% ammonia to afford 900 mg (70%) of desired compound; ¹H NMR (Free base, CDCl₃), δ 1.4 (s, 9H, t-butyl), 2.7-2.9 (br s, 4H), 2.7 (s, 3H), 3.8(s, 2H), 4.5 (s, 2H), 6.1-6.2 (dd, 1H), 6.7-6.8 (d, 2H), 6.9-7.0 (t, 3H), 7.1-7.4 (complex, 5H, aromatic), MS(FAB) m/z 452, which was used in the 20 next step by adding 4.0 mL of 4N HCl, 4 drops of anisole and stirring overnight at room temperature. TLC indicated the reaction was incomplete. The solution was heated to 50°C for 24 hours. The reaction mixture was concentrated *in vacuo* and the residue was azeotroped with toluene. The crude product was dissolved in triturated with diethyl ether to give 730 mg (93%) of 25 3ee as the free acid; mp 105-108°C; ¹H NMR (HCl salt, DMSO-d₆) δ 1.9-2.4 (br s, 4H, -CH₂CH₂-), 2.9 (s, 3H, NCH₃)3.8-4.1 (m, 3H), 4.5-4.7 (d, 2H), 6.2 (dd, 1H), 6.8 (d, 1H), 6.9 (t, 1H), 7.1-7.3 (complex, 7H, aromatic). MS(FAB) m/z 396. Anal (C,H,N) Calc. for C₂₃H₂₈N₂O₄·HCl·0.75 H₂O: C, 63.81; H, 6.75; N, 6.47. Found C, 61.87; H, 6.84; N, 6.19.

Example 3ff2-[4-Trifluoromethylphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-3-hydroxy-pyrrolidinyl]ethyl]acetamide hydrochloride

5 The compound **3ff** was prepared from N-methyl-N-[(1S)-1-phenyl-2-((3S)-3-hydroxypyrrolidine-1-yl)ethyl]-2-aminophenylacetamide² and 4-trifluoromethylphenyl acetic acid in 54 % yield; mp 217-219°C (d); ¹H NMR (free base, 200, MHz, CDCl₃) δ 1.88 (m, 2H), 2.35 (m, 3H), 2.85 (s, 3H), 2.50-3.35 (m, 4H), 3.98 (m, 2H), 4.10 (m, 1H), 6.00 (m, 1H), 7.30 (m, 5H), 7.55 (d, J = 9.0 Hz, 2H), 7.77 (d, J = 9.5 Hz, 2H). Anal. Calcd. for C₂₂H₂₅F₃N₂O₂.HCl: C, 59.66; 10 H, 5.92; N, 6.32. Found: C, 59.45; H, 5.68; N, 5.98.

Example 3gg2-(2-Pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-3-hydroxy-pyrrolidinyl]ethyl]acetamide dihydrochloride

15 The compound **3gg** was prepared as above from 2-pyridyl acetic acid in 38% yield; mp 180-182°C (d); ¹H NMR (free base, 200, MHz, CDCl₃) δ 1.78 (m, 2H), 2.10-2.65 (m, 3H), 2.75 (s, 3H), 2.88-3.20 (m, 4H), 3.95 (d, J = 13.0 Hz, 1H), 4.10 (d, J = 13.5 Hz, 1H), 4.20 (m, 1H), 6.05 (m, 1H), 7.20 (m, 7H), 7.60 (t, J = 7.0 Hz, 1H), 8.35 (d, J = 6.5 Hz, 1H). Anal. Calcd. for 20 C₂₀H₂₅N₃O₂.2HCl.0.25H₂O: C, 57.63; H, 6.65; N, 10.8. Found: C, 57.73; H, 6.79; N, 9.83.

Example 3hh2-(5-Bromo-3-pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-pyrrolidinyl ethyl]acetamide hydrochloride

25 Compound **3hh** was prepared using the general EDCI/DIPEA coupling procedure from USP 5,688,955 with, (1S)-N-methyl-2-pyrrolidino-1-phenethylamine (200 mg; 0.98 mmol), 5-bromo-3-pyridylacetic acid (231 mg; 1.07 mmol), HOBT (145 mg; 1.07 mmol), EDCI (204 mg; 1.07 mmol), and DIPEA (0.26 mL; 1.47 mmol). The reaction solution was allowed to stir at room 30 temperature overnight. TLC (95:5 methylene chloride: methanol with 2% ammonia) indicated the reaction was complete. The reaction was quenched with sat. sodium bicarbonate and the layers were separated. The organic layer was washed with brine and dried (anh. Na₂SO₄), filtered and evaporated. The crude product was purified by flash chromatography using a stepwise gradient of 2% to 4% MeOH: methylene chloride with 2% ammonia to afford 337 mg (85%) of 35 pure product which was treated with 1.0 M HCl in diethyl ether to give **3hh** as the HCl salt; mp

228-230°C; ^1H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.8 (s, 3H, NCH₃), 4.1-4.2 (br m, CH₂), 6.1-6.2 (br d, 1H, CH), 7.2-7.5 (complex, 5H, aromatic), 8.0-8.1 (br s, 1H, pyridyl), 8.5 (s, 1H, pyridyl), 8.6 (s, 1H, pyridyl); MS(FAB) m/z 401. Anal. (C,H,N) Calcd. for C₂₀H₂₄N₃OBr · HCl: C, 54.75; H, 5.74; N, 9.58. Found: C, 54.66; H, 5.71; N, 9.41.

5

Example 3ii

2-(5-Bromo-3-pyridyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-(3S)-3-hydroxy-pyrrolidinyl)ethyl]acetamide hydrochloride

10 The compound 3ii was prepared from 5-bromo-3-pyridyl acetic acid following the procedures described above in 44% yield; mp 144-146°C; ^1H NMR (free base, 200, MHz, CDCl₃) δ 1.66 (m, 2H), 2.00-2.50 (m, 3H), 2.77 (s, 3H), 2.88-3.40 (m, 4H), 3.80(d, J = 13.0 Hz, 1H), 3.95 (d, J = 13.5 Hz, 1H), 4.35 (m, 1H), 6.15 (m, 1H), 7.20 (m, 5H), 7.75 (s, 1H), 8.50 (s, 1H), 8.85 (s, 1H). Anal. Calcd. for C₂₀H₂₄BrN₃O₂.HCl.0.25H₂O: C, 51.79; H, 5.65; N, 9.06. Found: C, 51.96; H, 5.55; N, 8.76.

Example 3jj

2-(9-Anthracenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

20 The compound 3jj was prepared from 9-anthracene carboxylic acid as above in 34% yield; mp 273-275°C; ^1H NMR (200, MHz, CDCl₃) δ 2.00 (m, 4H), 2.67 (s, 3H), 3.00 (m, 1H), 3.45 (m, 1H), 3.88 (m, 1H), 4.40 (m, 2H), 5.80 (m, 1H), 7.43 (m, 8H), 7.88 (m, 5H), 8.38 (s, 1H). Anal. Calcd. for C₂₈H₂₈N₂O.HCl.0.25H₂O: C, 74.82; H, 6.61; N, 6.23. Found: C, 75.00; H, 6.60; N, 6.26.

Example 3kk

2-(2-Carboxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

30 To a solution of (S)-1-[(2-methylamino-2-phenyl)ethyl]pyrrolidine¹ (1.0 g, 5.21 mmol) in anhydrous THF (5 mL) under a nitrogen atmosphere was added homophthalic anhydride (0.845 g, 5.21 mmol) and the reaction mixture was stirred at room temperature for 4 days. The resulting solid was filtered, washed with THF and HCl salt was prepared by usual fashion to give 3kk (1.0 g, 50%); mp 230-232°C (d); MS (FAB) 367 (M+1); ^1H NMR (200, MHz, DMSO-d₆) δ 2.07 (m,

4H), 2.92 (s, 3H), 3.30-3.98 (m, 5H), 4.00 (d, J = 14.0 Hz, 1H), 4.18 (m, 1H), 4.43 (d, J = 14.0 Hz, 1H), 6.15 (m, 1H), 7.30-7.65 (m, 8H), 8.00 (d, J = 8.0 Hz, 1H) . Anal. Calcd. for $C_{22}H_{26}N_2O_3.HCl$: C, 65.58; H, 6.75; N, 6.96; Cl, 8.81. Found: C, 65.52; H, 6.81; N, 7.04; Cl, 8.81.

5

Example 3ll

[2-(2-Phenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamido]2-oxo-glycine hydrochloride

10 To a suspension of **3ff** was condensed with glycine t-butyl ester hydrochloride following the general procedure to give the intermediate in 55% yield. The t-butyl group was removed by 4N HCl to give the desired product which was recrystallized from acetonitrile to give **3ll** in 93% yield; mp 235-236°C; MS (FAB) 424 (M+1); 1H NMR (200, MHz, DMSO-d₆) δ 1.95 (m, 4H), 2.72 (s, 3H), 3.35-4.25 (m, 11H), 6.18 (m, 1H), 7.20-7.65 (m, 8H), 8.70(m, 1H) . Anal. Calcd. for
15 $C_{24}H_{29}N_3O_4.HCl.0.75H_2O$: C, 60.88; H, 6.71; N, 8.87. Found: C, 60.97; H, 6.65; N, 8.91.

Example 3mm

Methyl N-[2-(2-phenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamido]2-oxo-glycinate hydrochloride

20 To a solution of **3ff** (0.50 g, 1.05 mmol) in anhydrous methanol (50 mL) was added Dowex[®] 50Wx4-400 (H⁺) resin (5.0 g, pre-washed with methanol). The reaction mixture was the stirred with refluxing under a nitrogen atmosphere for 48 h. The resin was removed by filtration washed with excess of hot methanol and the combined mehanolic solution was evaporated to dryness. The residue was redissolved in CH₂Cl₂ and concentrated to a small volume and addition of anhydrous ether resulted the compound **3mm** (0.12 g, 24%); mp 204-206°C; MS (FAB) 438 (M+1); 1H NMR (200, MHz, CDCl₃), δ 1.85-2.45 (m, 6H), 2.75-3.25 (m, 2H), 2.92 (s, 3H), 3.75 (s, 3H), 3.80-4.25 (m, 7H), 6.25 (bs, 1H), 7.15-7.77(m, 9H) . Anal. Calcd. for $C_{25}H_{31}N_3O_4.HCl.0.25H_2O$: C, 62.75; H, 6.85; N, 8.78. Found: C, 62.65; H, 6.87; N, 8.60.

30

Example 3nn2-(3,4-Dihydroxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

5 The compound was prepared from 3,4-dihydroxyphenyl acetic acid in 12% yield; mp 227-229°C (d); ¹H NMR (300, MHz, DMSO-d₆) δ 1.90 (m, 4H), 2.70 (s, 3H), 3.05-3.20 (m, 2H), 3.35 (bs, 2H), 3.45-3.70 (m, 4H), 4.50 (m, 1H), 6.12 (m, 1H), 6.45 (d, J = 8.1 Hz, 1H), 6.62 (m, 2H), 7.18 (d, J = 7.5 Hz, 2H), 7.32 (m, 3H), 8.73 (bs, 1H), 8.83 (bs, 1H). Anal. Calcd. for C₂₁H₂₆N₂O₃.HCl.0.25H₂O: C, 63.79; H, 7.01; N, 7.08. Found: C, 63.59; H, 6.89; N, 7.15.

10

Example 3oo2-(3,4-Dimethoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

15 The compound was prepared from 3,4-dimethoxyphenyl acetic acid in 65% yield; mp ; 240-242°C; ¹H NMR (300, MHz, CDCl₃) δ 2.00-2.35 (m, 4H), 2.85(s, m, 5H), 3.26 (m, 1H), 3.18 (s, m, 7H), 4.05 (m, 4H), 6.36 (m, 1H), 6.81 (m, 2H), 6.93 (s, 1H), 7.19 (m, 2H), 7.36 (m, 3H). Anal. Calcd. for C₂₃H₃₀N₂O₃.HCl: C, ; H, 7.01; N, 7.08. Found: C, 63.59; H, 6.89; N, 7.15.

20

Example 3pp2-(2-Methanesulfonamidophenyl)-N-methyl-N-[(1S)-1-(3-methanesulfon-amidophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide Hydrochloride(1) 2-(2-Nitrophenyl)-N-methyl-N-[(1S)-1-(3-nitrophenyl)-2-(1-pyrrolidinyl)-ethyl]acetamide

25 A solution of 2-nitrophenylacetic acid (1.99 g, 11.0 mmol) and 1-hydroxybenzotriazole (1.49 g, 11.0 mmol) in CH₂Cl₂ (50 ml) was cooled in an ice bath. To this slurry was added EDCI, and the solution turned brown clear after 30 minutes at room temperature. A solution of (2s)-1-[2-(methylamino)-2-(3-nitrophenyl)ethyl]pyrrolidine¹ (2.49 g, 10.0 mmol) in CH₂Cl₂ (5 ml) was added, followed by DIPEA. The solution was stirred in ice bath for 30 minutes and then at room temperature for 18 hours. The reaction was quenched by adding saturated aqueous 30 NaHCO₃ (20 ml) and stirred for 10 minutes. After separation, the organic layer was washed with water, brine, dried (Na₂SO₄). The solvent was removed via rotary evaporation and the brown residue was purified by silica column chromatography [2% MeOH/CH₂Cl₂ (2%NH₃)] to give the product (2.4 g, 58%).

(2) 2-(2-Aminophenyl)-N-methyl-N-[(1R, S)-1-(3-aminophenyl)-2-(1-pyrrolidinyl)ethyl]acetamide

A suspension of above compound (475 mg, 1.15 mmol) and Raney nickel (50% slurry in water) in ethanol (10 ml) was heated at 50 °C and treated with a solution of hydrazine hydrate (360 ml, 11.5 mmol) in ethanol (2 ml). Upon addition of the reagent, effervescent occurred. The mixture was then stirred at 50 °C for 0.5 h. After cooling, the mixture was filtered through a bed of celite, and the catalyst was washed with hot methanol (10 ml). The combined filtrate and washing was evaporated and dried in vacuum (388 mg, 95%). ¹H NMR (DMSO-d₆): δ 1.64 (bs, 4H), 2.40 (bs, 2H), 2.58 (m, 2H), 2.66 (s, 3H), 3.06-3.59 (m, 4H), 4.95 (s, 2H), 5.01 (s, 2H), 5.77 (dd, J=4.9, 11.4 Hz, 1H), 6.39-6.48 (m, 4H), 6.63 (d, J=7.6 Hz, 1H), 6.89-7.04 (m, 3H).

To a solution of the diamine (388 mg, 1.11 mmol) in CH₂Cl₂ (10 ml) cooled in an ice bath was added pyridine (540 ml, 6.67 mmol), followed by MsCl (190 ml, 2.45 mmol) in CH₂Cl₂ (5 ml). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 18 hours. The solution was washed with saturated aqueous NaHCO₃ (2x50 ml), brine, dried (Na₂SO₄). The solvent was removed by rotary evaporation and the residue was purified by silica column chromatography to give gummy foam after drying (383 mg, 68%) which was then converted to the HCl salt form. mp: 160 °C (d). ¹H NMR (DMSO-d₆): δ 1.96 (bs, 4H), 2.77 (s, 3H), 2.97 (s, 3H), 2.98 (s, 3H), 3.14 (m, 2H), 3.57 (m, 3H), 3.97-4.10 (m, 3H), 6.12 (d, J=10.8 Hz, 1H), 7.03-7.37 (m, 8H), 9.10 (s, 1H), 9.81 (s, 1H). Fab MS (MH⁺): 509. Anal. Calcd. for C₂₃H₃₃N₄O₅S₂Cl: C, 48.47; H, 6.43; N, 9.50. Found: C, 48.57; H, 6.07; N, 9.25.

Example 3qq

2-(2-Iso-butyramidophenyl)-N-methyl-N-[(1S)-1-(3-isobutyramido-phenyl)-2-(1-pyrrolidinyl)ethyl]acetamide Methanesulfonic acid salt

To a solution of the diamine (132 mg, 0.376 mmol) in CH₂Cl₂ (5 ml) cooled in an ice bath was added pyridine (182 ml, 2.26 mmol), followed by isobutyryl chloride (119 ml, 1.14 mmol) in CH₂Cl₂ (5 ml). The mixture was stirred at 0 °C for 0.5 h and then at room temperature for 18 hours. The solution was washed with aqueous saturated NaHCO₃ (2x25 ml), brine, dried (Na₂SO₄). TLC indicated that the compound was contaminated by bis-acylated side product. Thus, the solvent was removed by rotary evaporation and the residue was dissolved in MeOH (2 ml), treated with a drop of NaOH (13 N), and stirred at room temperature for 5 minutes. After

neutralization with HCl (6N), the solvent was evaporated, the residue was purified by silica column chromatography to give a gummy foam after drying which was then converted to methanesulfonic acid salt (178 mg, 76%). Mp:143-145 °C; ¹H NMR (DMSO-d₆): δ 1.08 (m, 12H), 1.88 (m, 2H), 2.00 (m, 2H), 2.31 (s, 3H), 2.56 (m, 2H), 2.65 (s, 3H), 3.18 (m, 2H), 3.36-5 3.63 (m, 6H), 3.80 (d, J=16.2 Hz, 1H), 4.10 (m, 1H), 6.09 (d, J=10.8 Hz, 1H), 6.90 (d, J=7.6 Hz, 1H), 7.10-7.63 (m, 7H), 9.20 (bs, 1H), 9.41 (s, 1H), 9.92 (s, 1H). Fab MS (MH⁺): 493. Anal. Calcd. for C₃₀H₄₄N₄O₆S: C, 58.86; H, 7.67; N, 9.15. Found: C, 58.77; H, 7.51; N, 8.98.

Example 3rr

10 4-[4-N-Methylsulfonamido-phenyl]-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)-ethyl]acetamide hydrochloride

4-(N,N-Dimethylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (for preparation see USP 5,688,955) 1.3 g; 2.63 mmol was dissolved in 60 mL of 2:1 MeOH: THF and 2.0 mL of 10 M NaOH was added. After 20 minutes, TLC (95:5 methylene chloride: methanol with 2% ammonia) indicated the reaction was complete. The reaction was neutralized with 10% HCl and concentrated *in vacuo*. The residue was dissolved in methylene chloride and washed with 10% sodium bicarbonate, brine and dried (anh. Na₂SO₄). The organic layer was concentrated *in vacuo* and the crude product was purified by flash chromatography using a stepwise gradient of 2% to 8% MeOH: methylene chloride with 2% ammonia to give 300 mg (28%) of desired product, which was treated with 1.0 M HCl in diethyl ether to afford 3rr as a tan solid. mp >260°C(dec.); ¹H NMR (HCl salt, DMSO-d₆) δ 2.0 (br s, 4H, -CH₂CH₂-), 2.8(s, 3H, NCH₃), 3.0(s, 3H, SO₂CH₃), 3.8-4.0(m, 2H), 6.1-6.3(dd, 1H), 7.1-15 7.5(complex, 9H, aromatic), 9.7(s, 1H). MS(FAB) m/z 415. Anal. (C,H,N) Calcd. for C₂₂H₂₉N₃O₃S·HCl·0.25 H₂O: C, 58.46; H, 6.69; N, 9.30. Found: C, 57.89; H, 6.64; N, 9.19.

Example 3ss

20 2-(3,4-Dichlorocinnamyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)-ethyl]acetamide hydrochloride

30 The compound was prepared from 3,4-dichlorocinnamic acid in 70% yield; mp 220-222°C; Anal. Calcd. for C₂₂H₂₄Cl₂N₂O·HCl: C, 60.08; H, 5.73; N, 6.37. Found: C, 60.25; H, 5.81; N, 6.28.

Example 3tt2-(2-Nitrocinnamyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

5 The compound was prepared from 2-nitrocinnamic acid in 46% yield; mp 195-197°C;
Anal. Calcd. for C₂₂H₂₅N₃O₃.HCl: C, 63.53; H, 6.30; N, 10.10. Found: C, 63.25; H, 6.38; N,
10.08.

Example 3uu

10 (R,S)-1- [2-(Methanesulfonylamino) phenyl-N-methylacetamido]-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane, methanesulfonic acid salt
(R,S)-3-Methoxy-phenylglycine (5, Scheme M)

15 NaCN (12.2 g, 0.249 mol) was dissolved in 50 ml of water, and to this solution was added ammonium chloride (13.3 g, 0.249 mol). When all had dissolved, a solution of m-anisaldehyde (33.8 g, 0.249 mol) in 50 ml of EtOH was added slowly. The mixture was stirred at ambient temperature for 2-3 hours. TLC indicated no starting material left. The mixture was taken up in water/toluene (50ml /50 ml). The organic layer was washed with water (50 ml), extracted with 6N HCl (2x30 ml). To hydrolyze the amino cyanide, the hydrochloric extract was refluxed for 20 4~5 hours. The solution was cooled to room temperature and filtered from some tarry material. The filtrate was cooled in ice bath and the aminoacid salt was collected via filtration, washed with cold water (20 ml), ether, dried at 60 degrees overnight to give 5 (14.5 g, 27%); NMR (DMSO-d₆), δ 3.7 (3H, s), 4.29 (1H, s), 6.87 (1H, m), 6.96 (1H, d, J=7.6 Hz), 6.98 (1H, s), 7.26 (1H, t, J=8.0 Hz).

25

(R,S)-N-Methoxycarbonyl-2-(3-methoxyphenyl)glycine (6)

(R,S)-3-Methoxy-phenylglycine (5, 14.5 g, 66.7 mmol) was dissolved in NaOH (1N, 233ml, 233 mmol) and the solution was cooled in ice bath for 15 minutes. To this solution was added methyl chloroformate (7.73 ml, 100 mmol) dropwise. After the addition was complete, the 30 mixture was stirred at room temperature for 2 hours. The pH was adjusted to 10 with 2N NaOH and the stirring was continued for 1 hour. The solution was washed with ether (2x100 ml), acidified with 6N HCl after addition of EtOAc (100 ml). The aqueous layer was extracted with EtOAc (100 ml), and the combined organic extracts were washed with brine (100 ml), dried over (Na₂SO₄), concentrated to yellow syrup 6, (14.4 g, 90%). NMR (CDCl₃), δ 3.70 (3H, s), 3.82 (3H, s), 5.35 (1H, d), 5.77 (1H, d), 6.87-7.01(3H, m), 7.31(1H, t).

(R,S)-N-Methoxycarbonyl-2- (3-methoxyphenyl) glycine, pyrrolidine (7)

(R,S)-N-Methoxycarbonyl-2-(3-methoxyphenyl) glycine (6, 14.4 g, 60.4 mmol) and HOBt (8.97 g, 66.4 mmol) were dissolved in THF (150 ml) and cooled in ice bath. To this 5 solution was added a solution of DCC (12.4 g, 60.4 mmol) in THF (50 ml). After stirring at room temperature for 2 hours, the mixture was cooled in ice bath, and the resulting DCU was filtered, washed with cold THF. The filtrate was treated with a solution of pyrrolidine (5.0 ml, 60.4 mmol) in dichloromethane (50 ml). The solution was stirred at room temperature for 18 hours and concentrated. The residue was taken up in EtOAc (250 ml), and the mixture was washed 10 with NaHCO₃ (saturated, 200 ml), water, brine, dried over Na₂SO₄, concentrated to a pale solution (50 ml) which was stored in refrigerator overnight. The more precipitated DCU was filtered off, and the filtrate was dried to give a pale yellow oil 7, (12.8 g, 77%). NMR (CDCl₃), δ 1.8 (4H, m), 3.4-3.6 (4H, m), 3.65 (3H, s), 3.8 (3H, s), 5.35 (1H, d), 6.8-7.0 (3H, m), 7.3 (1H, m).

15 (R,S)-1- (3-Methoxyphenyl)-1-methylamino-2- (1-pyrrolidino) ethane (8)

LiAlH₄ (5.3 g, 140 mmol) was stirred in anhydrous THF (200 mL) under N₂ and a solution of (R,S)-N-Methoxycarbonyl-2- (3-methoxyphenyl) glycine, pyrrolidine (12.8 g, 46.6 mmol) in THF (100 ml) was added over 30 minutes at 10~15 degree. The mixture was stirred at room temperature for 0.5 hour then at 55 degree for 2 hours. After cooling in ice bath the 20 mixture was carefully quenched with excess saturated NaHCO₃, filtered. The filtrate was washed with brine, dried over Na₂SO₄, and evaporated to 10.0 grams of colorless oil (8) that was used in further reaction without purification.

25 (R,S)-1- (2-Nitrophenyl-N-methylacetamido)-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane (9)

A solution of 2-Nitrophenylacetic acid (1.99 g, 11.0 mmol), HOBt (1.49 g, 11.0 mmol) in THF (50 ml) was cooled in ice bath and treated with a solution of DCC (2.27 g, 11.0 mmol) in THF (5 ml). The mixture was warmed up to room temperature and stirred for 2 hours. After cooling in ice bath the precipitated DCU was filtered, and the filtrate was treated with a solution of (R,S)-1-(3-Methoxyphenyl)-1-methylamino-2- (1-pyrrolidino) ethane (8) in CH₂Cl₂ (10 ml). The solution was stirred in N₂ at room temperature for 18 hours and concentrated. The residue 30 was dissolved in EtOAc (100 ml), washed with saturated NaHCO₃, brine, dried (Na₂SO₄). Removal of the solvent, followed by silica column chromatography yielded 3.0 grams of the product (9). NMR (CDCl₃), δ 1.74 (4H, bs), 2.52 (2H, bs), 2.67 (2H, bs), 2.77 (1H, m), 2.84 (3H,

s), 3.10 (1H, m), 3.83 (3H, s), 4.02-4.31 (2H, m), 6.03 (1H, dd, J = 6.0, 9.8 Hz), 6.80-6.94 (3H, m), 7.26 (1H, m), 7.39-7.46 (2H, m), 7.54-7.59 (1H, m), 8.10 (1H, dd, J = 1.2, 8.0 Hz).

(R,S)-1- (2-Aminophenyl-N-methylacetamido)-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane

5 A suspension of (R,S)-1-(2-nitrophenyl-N-methylacetamido)-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane (8) (1.3 g, 3.27 mmol) and Raney Ni (1 spatula) in EtOH (20 ml) was stirred at 50 degree and treated with a solution of hydrazine hydrate in EtOH (10 ml). After effervescent stopped, the mixture was stirred at 55 degree for 0.5 hour, then cooled to room temperature, filtered through a bed of celite, washed with hot MeOH (20 ml). The combined filtrate and 10 washing was concentrated, dried to yellow residue (1.2 g) of amino compound that was used with further purification.

(R,S)-1- [2-(Methanesulfonylamino) phenyl-N-methylacetamido]-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane, methanesulfonic acid salt (3uu)

15 To a solution of (R,S)-1-(2-aminophenyl-N-methylacetamido)-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane (1.2 g, 3.24 mmol) in CH_2Cl_2 (20 ml) was added pyridine (0.79 ml, 9.72 mmol), followed by a solution of MsCl (0.376 ml, 4.86 mmol). The mixture was stirred at room temperature for 18 hours. The mixture was washed with water (20 ml), brine, dried (Na_2SO_4). The solution was concentrated, and the residue was purified via silica column chromatography to 20 give a yellowish oil (1.20 g, 83%). 251 mg of the free base was converted to methane sulfonic acid salt, 3uu. M p: 135 °C (decomposed). NMR (DMSO-d_6), δ 1.92 (2H, bs), 2.02 (2H, bs), 2.32 (3H, s), 2.72 (3H, s), 2.97 (3H, s), 3.19 (2H, m), 3.56-3.97 (8H, m), 4.03-4.12 (2H, m), 6.08 (1H, d, J = 12.0 Hz), 6.74 (1H, s), 6.81 (1H, dd, J = 2.3, 8.0 Hz), 7.16-7.39 (5H, m), 9.07 (1H, s), 9.26 (1H, bs). MS (FAB) m/z 446. Anal. (C, H, N) $\text{C}_{23}\text{H}_{31}\text{N}_3\text{O}_4\text{S} \cdot \text{CH}_3\text{SO}_3\text{H} \cdot 0.2\text{H}_2\text{O}$.

25

Example 3vv

(R,S)-1-[2-(Methanesulfonylamino) phenyl-N-methylacetamido]-1-(3-hydroxyphenyl)-2-(1-pyrrolidino)-ethane, methanesulfonic acid salt

30 A solution of (R,S)-1-[2-(methanesulfonylamino)phenyl-N-methylacetamido]-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane (3uu, 196 mg, 0.440 mmol) in CH_2Cl_2 (15 ml) was cooled to -70 degree and treated with a solution of BBr_3 (1.0 M in CH_2Cl_2 , 1.45 ml, 1.45 mmol) in CH_2Cl_2 (2 ml). The mixture was stirred at -70 degree for 1 hour, then slowly warmed up to room temperature overnight. The mixture was carefully quenched at 0 degree with MeOH (5 ml) 35 and the solution was evaporated under reduced pressure. The residue was stirred in 10 ml of

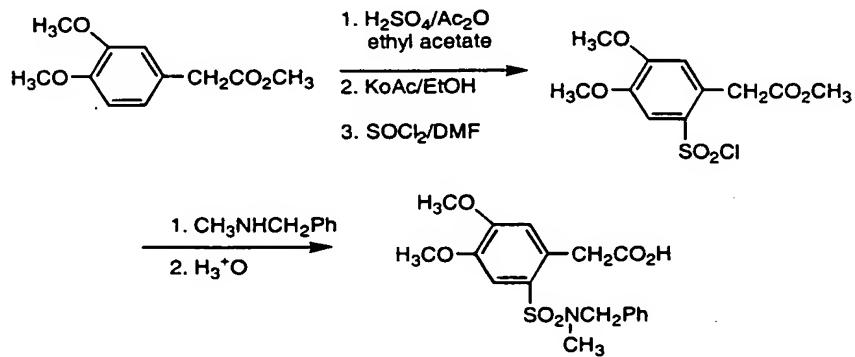
anhydrous MeOH/Et₂O (1/1) for 6 hours and filtered. The white solid was taken up in CHCl₃ (50 ml) and NaHCO₃/Na₂CO₃ (pH~10)(50 ml). The organic layer was washed with brine, dried (Na₂SO₄). After removal of the solvent, the residue was dissolved in MeOH (5 ml) and treated with CH₃SO₃H (0.026 ml, 0.404 mmol). The solvent was evaporated and the residue was 5 sonicated in ether. The precipitate was filtered, dried to give 3vv, (0.164 g, 84%). mp: 232-234 °C. NMR (DMSO-d₆), δ 1.93 (2H, bs), 2.02 (2H, bs), 2.32 (3H, s), 2.70 (3H, s), 2.97 (3H, s), 3.16 (2H, bs), 3.40-3.80 (4H, m), 4.03-4.12 (2H, m), 6.04 (1H, d, J = 9.6 Hz), 6.63-6.72 (3H, m), 7.14-7.39 (5H, m), 9.06 (1H, s), 9.21 (1H, bs), 9.56 (1H, s). MS (FAB) m/z 432. Anal. (C, H, N) C₂₂H₂₉N₃O₄S.CH₃SO₃H.0.2H₂O.

10

Example 3ww

2-(3-Indolyl)-N-methyl-N-[{(1S)-1-phenyl-2-[(3S)-1-pyrrolidin-3-ol]ethyl}-acetamide hydrochloride

15 Compound 3ww was prepared from indole-3-acetic acid (477 mg; 2.72 mmol), DCC (1.12 g; 5.44 mmol), pyridine (0.440 mL; 5.44 mmol) and S-(-)-3-pyrrolidinol (600 mg; 2.72 mmol, for preparation see EP 0398 720 A2) in 15 mL of dry methylene chloride. After stirring at room temperature for 24 h, TLC (95:5 methylene chloride:methanol w/2% ammonia) indicated the reaction was complete. The reaction was quenched with sat. sodium bicarbonate and the 20 layers were separated. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and conc. *in vacuo* to give 2.04 g of a viscous yellow oil which was purified by flash chromatography using a stepwise gradient of 2% to 3% methanol: methylene chloride with 2% ammonia to yield 700 mg (69%) of desired compound which was converted to the hydrochloride salt with HCl/ether to give 720 mg of 3ww. m.p. 142 °C(dec.); ¹H NMR (HCl salt, CDCl₃, 300 MHz) δ 2.1 (br, m, 4H), 2.8 (s, 3H), 4.5 (m, 1H), 6.3 (br, m, 1H), 7.2 (br, m, 1H), 7.3 (complex, 4H, aromatic), 7.5-7.6 (d, 2H), 7.8 (d, 2H). Fab MS (MH⁺): 377. Anal. Calcd for 25 C₂₃H₂₇O₂N₃·HCl: C, 63.29; H, 7.04; N, 9.63. Found C, 63.15; H, 7.03; N, 9.57.

Example 3xx2-(2-N-Benzyl-2-N-methylsulfamoyl-3,4-dimethoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride

5

Compound **B** was prepared from methyl 3,4-dimethoxyphenyl acetate following the literature procedure [J. Het. Chem. 29, 1667 (1992)] and condensed with the diamine in usual fashion to give **3xx** in 60% yield; mp 188-190°C; ¹H NMR (300 MHz, CDCl₃) δ 1.88 (m, 4H), 2.64 (s, 3H), 2.85-3.25 (m, 4H), 2.91 (s, 3H), 3.90 (s, 3H), 3.94-4.28 (m, 2H), 3.95 (s, 3H), 4.30-4.60 (m, 4H), 6.48 (m, 1H), 7.15-7.40 (m, 11H), 7.55 (s, 1H). Anal. Calcd. for C₃₁H₃₉N₃O₅S·HCl·0.5 H₂O: C, 60.92; H, 6.76; N, 6.88. Found: C, 60.73; H, 6.99; N, 6.82.

15

Example 3yy2-(N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-[(1R)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide methane sulfonate

Compound **3yy** was prepared using the same synthetic scheme as described in USP 5, 688,955 using (R)-1-[2-methylamino-2-phenyl]ethyl pyrrolidine (for preparation see J. Med. Chem. 34, 1991 pp181, Costello, G.F. et. al. m.p. 179-181) C: ¹H NMR (Mesylate salt, CDCl₃, 300 MHz) δ 2.0-2.2 (br, m, 4H), 2.8 (s, 3H), 3.0 (s, 3H), 3.6 (d, 2H), 6.2-6.3 (d, 1H), 7.1 (m, 3H), 7.2 (m, 1H), 7.3 (m, 3H), 7.7 (d, 2H). Fab MS (MH⁺): 415. Anal. Calcd. for C₂₃H₃₃O₆N₃S₂: C, 53.99; H, 6.50; N, 8.21. Found C, 53.98; H, 6.41; N, 8.10.

25

Example 3zz(R,S)-1- (4-Trifluoromethylphenyl-N-methylacetamido)-1-(3-methoxyphenyl)-2-(1-pyrrolidino)-ethane, methanesulfonic acid salt

5 The procedure is the same as that of **3uu**. Yield: 74%. Mp.: 166-168 °C. .NMR (CDCl₃),
 δ : 2.11 (2H, m), 2.16-2.32 (2H, m), 2.81 (3H, s), 2.85-2.98 (4H, m), 3.12-3.21 (1H, m), 3.75
(3H, s), 3.83 (1H, m), 4.05-4.33 (4H, m), 6.30 (1H, dd, J = 2.6, 12.0 Hz), 6.67 (1H, d, J = 1.8
Hz), 6.75 (1H, d, J = 7.6 Hz), 6.87 (1H, dd, J = 2.4, 8.3 Hz), 7.30 (1H, m), 7.45 (1H, d, J = 8.1
Hz), 7.57 (1H, d, J = 8.1 Hz). MS (FAB) m/z 421. Anal. (C, H, N) C₂₃H₂₇N₂O₂F₃.CH₃SO₃H.

10

Example 3aaa(R,S)-1- (4-Trifluoromethylphenyl-N-methylacetamido)-1-(3-hydroxyphenyl)-2-(1-pyrrolidino)-ethane, methanesulfonic acid salt

15 The procedure is the same as that of **3vv**. Yield: 38.5%. Mp: 158-160 °C. NMR (CDCl₃),
 δ : 2.01-2.14 (4H, m), 2.73 (3H, s), 2.82 (3H, s), 2.94 (2H, m), 3.30 (1H, m), 3.76 (1H, m), 4.03-
4.14 (4H, m), 6.20 (1H, dd, J = 3.3, 11.0 Hz), 6.63 (1H, d, J = 7.9 Hz), 6.86 (1H, dd, J = 1.8, 8.0
Hz), 7.06 (1H, s), 7.18 (1H, t, J = 8.0 Hz), 7.41 (2H, d, J = 8.0 Hz), 7.56 (2H, d, J = 8.0 Hz).).
MS (FAB) m/z 407. Anal. (C, H, N) C₂₂H₂₅N₂O₂F₃.1.1CH₃SO₃H.

20

Example 3bbb2-Fluorophenyl-N-methyl-N- [(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-acetamide hydrochloride

25 Compound **3bbb** was prepared using the same general EDCI/DIPEA coupling procedure as described in USP 5,688,955 with 2-fluorophenylacetic acid (415 mg; 2.69 mmol), HOBT(363 mg; 2.69 mmol), EDCI (514 mg; 2.69 mmol), N,N-diisopropylethylamine (0.63 mL; 3.66 mmol), and (1S) 1-[(2-methylamino-2-phenyl)ethyl]pyrrolidine(500 mg; 2.44 mmol) in 10 mL of dry methylene chloride at room temperature. After 24 h, TLC(95:5 methylene chloride:methanol
30 w/2% ammonia) indicated the reaction was complete. The reaction solution was quenched with sat. sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried over anh. sodium sulfate, filtered and conc. *in vacuo* to give 900 mg of a dark brown oil which was purified by flash chromatography using a stepwise gradient of 2% to 4% methanol:methylene chloride with 2% ammonia to yield 750 mg (90%) of desired product which
35 was converted to the hydrochloride salt with HCl/ether to give 880 mg of **3bbb**. m.p.
255°C(dec.); ¹H NMR (HCl salt, CDCl₃, 300 MHz) δ 2.0 (br, m, 4H), 2.1-2.2 (br, m, 2H), 2.9 (s,

3H), 3.8-4.0 (dd, 4H), 7.0-7.4 (complex, 9H, aromatic). *Fab MS (M⁺)*: 340. *Anal. Calcd. for C₂₁H₂₅ON₂FHCl* : C, 66.97; H, 6.95; N, 7.43. *Found* C, 66.76; H, 6.90; N, 7.43.

Example 3ccc

4-Fluorophenyl-N- methyl-N-[*(1S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide hydrochloride (3ccc)

Compound **3ccc** was prepared using the same general EDCI/DIPEA coupling procedure from USP 5,688,955 with 4-fluorophenylacetic acid (415 mg; 2.69 mmol), HOBT (363 mg; 2.69 mmol), EDCI (514 mg; 2.69 mmol), N,N-diisopropylethylamine (0.63 mL; 3.66 mmol) and (1S) 1-[(2-methylamino-2-phenyl)ethyl]pyrrolidine (500 mg; 2.44 mmol) in 10 mL of dry methylene chloride at room temperature. After 24h, TLC (95:5 methylene chloride:methanol w/2% ammonia) indicated the reaction was complete. The reaction was quenched with sat. sodium bicarbonate and the layers were separated. The organic layer was washed with brine, dried over anh. sodium sulfate, filtered and conc. *in vacuo* to give 900 mg of a dark brown oil which was purified by flash chromatography using a stepwise gradient of 2% to 3% methanol: methylene chloride with 2% ammonia to yield 800 mg (96%) of desired product which was converted to the hydrochloride salt with HCl in ether to give **3ccc**. m.p. >260⁰C(dec.); ¹H NMR (HCl salt; CDCl₃, 300 MHz) δ 2.0 (br, m, 4H), 2.1-2.2 (br, m, 2H), 2.9 (s, 3H), 3.8-4.0 (dd, 4H), 7.0-7.4 (complex, 9H, aromatic). Fab MS (MH⁺): 340. Anal Calcd for C₂₁H₂₅ON₂·HCl : C, 66.82; H, 6.95; N, 7.43. Found C, 66.81; H, 6.94; N, 7.48

Example 3ddd

(E)- 4-[2-(2-Amino-4,5-dichlorophenyl)-N-methyl-N-[(1S)-1-phenyl]-2-[1-pyrrolidinyl]ethyl]acetamido]4-oxo-2-butenoic acid hydrochloride

To a solution of **3y** (1.4 g, 2.63 mmol) in THF:CH₃OH (1:1, 20 mL) at room temperature was added 1M LiOH aqueous solution (5.3 mL, 5.26 mmol) and the reaction mixture was stirred for 8 h. Progress of reaction was followed by TLC and reaction mixture was acidified to pH 4.0 from 1N HCl. The solvent was removed under reduced pressure. The residue was triturated with CH₂Cl₂ (3x45 mL). The combined organic layer was washed with sat. salt solution which resulted in the precipitation of the compound. The solid was filtered off, washed with a small amount of water, anhydrous ether, and dried to give **3ddd 0**, 0.85 g (59%); mp 205-207°C (d); ¹H NMR (300 MHz, DMSO-d₆) δ 1.93 (m, 4H), 2.84 (s, 3H), 3.00-3.75 (m, 6H), 3.98 (d, J = 15.0

Hz, 1H), 4.05 (m, 1H), 4.35 (d, J = 16.5 Hz, 1H), 6.12 (m, 1H), 6.65 (d, J = 15.4 Hz, 1H), 7.25-7.38 (m, 5 H), 7.55 (s, 1H), 7.79 (d, J = 15.0 Hz, 1H), 8.31 (s, 1H). Anal. Calcd. for $C_{25}H_{27}Cl_2N_3O_4 \cdot HCl \cdot NaCl \cdot 1.5 H_2O$: C, 47.94; H, 4.99; N, 6.71. Found: C, 47.98; H, 4.92; N, 6.57.

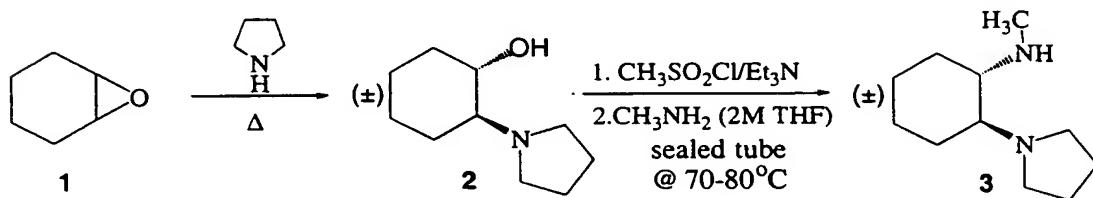
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Compounds of formula IV

Intermediates

The following intermediates were prepared.

Synthesis of Diamine 3



10

(\pm)-trans-2-Pyrrolidinyl-N-methylcyclohexylamine (3)

The racemic diamine (3) was prepared by a number of procedure reported in the literature.^{10,11} Alternatively, the amine was also prepared from cyclohexene oxide (1) following the procedure described in Scheme I and the literature¹² in 70% overall yield as brown oil. A sample was purified by the distillation (b.p. 75-82°C/ 1.0 mm, lit.² b.p. 76-80°C/1.2 mm); ¹H-NMR (200 MHz, $CDCl_3$) δ 1.04-1.36 (m, 4H), 1.49-1.89 (m, 8H), 2.18 (d, J = 5.0 Hz, 1H), 2.52 (s, 3H), 2.56-2.70 (m, 4H), 2.80-2.93 (m, 1H), 7.75 (bs, 1H). The corresponding chiral amine (3) could be prepared following the literature procedures.

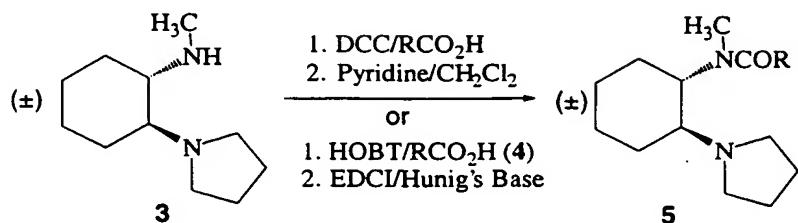
Ref.

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(11) DeCosata, B.; George, C.; Rothman, R. B.; Jacobson, A. E.; Rice, K. E. *FEBBS Lett.* **1987**, *223*, 335-339.

(12) Freeman, J. P.; Michalson, E. T.; D'Andrea, S. V.; Baczynskyj, L.; Von Voigtlander, P. F.; Lahti, R. A.; Smith, M. W.; Lawson, C. F.; Scahill, T. A.; Miszak, S. A.; Szmuszkovicz, J. *J. Med. Chem.* **1991**, *34*, 1891-1896.

5 Synthesis of Arylacetamides



10 General procedure for the preparation of aryl acetamides (\pm) 5 HCl

To a stirred solution of aryl acetic acid (**4**) (1.5 mmol) in 20 mL of dry CH_2Cl_2 was added pyridine (0.5 mmol) at $0\rightarrow 5^\circ\text{C}$ under a nitrogen atmosphere. N,N'-Dicyclohexyl-carbodiimide (2.0 mmol) was added in one portion and the reaction mixture was continued stirring for 30 min while warming to room temperature. A solution of the (\pm) **3** (1.0 mmol) in 10 mL of dry CH_2Cl_2 was added and the progress of the reaction was monitored by TLC in solvent system corresponds to $\text{CHCl}_3:\text{CH}_3\text{OH}:28\% \text{ NH}_4\text{OH}$ (93:5:2). After disappearance of the diamine **3**, the reaction mixture was quenched with saturated NaHCO_3 and stirring was continued for addition 15 min. The precipitated N,N'-dicyclohexylurea (DCU) was removed by filtration and the filter cake was washed with additional amounts of CH_2Cl_2 . The combined filtrate was evaporated to dryness and the residue was purified either on a silica gel column or using Chromatotran silica gel platters from the solvent system mentioned for each compound to give (\pm) **5** as free base. The hydrochloride salts were prepared from dissolving (\pm) **5** in minimum amount of CH_2Cl_2 and addition of 2.0 equivalents of 1M etherial HCl. The solvents were removed under reduced pressure and the HCl salts were recrystallized from the solvents indicated below. The yields given below are for overall steps.

Example 103(±)-trans-2-Nitro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide Hydrochloride [(±) 5a HCl]

5 Prepared from 2-nitrophenylacetic acid [solvent for purification- CH₂Cl₂:CH₃OH: 28%NH₄OH (98:2:2)]: yield 21% as a white solid (2-propanol); mp 267-269°C (d); ¹H NMR((200 MHz, CDCl₃) δ 1.00-1.44 (m, 2H), 1.60-2.35 (m, 8H), 2.85 (m, 1H), 3.15 (s, 3H), 3.18-3.35 (m, 4H), 3.40 (m, 1H), 3.85 (m, 1H), 4.33 (dd, J = 10.0 Hz, 2H), 4.64 (m, 1H), 7.35 (m, 1H), 7.56 (m, 2H), 8.05 (d, J = 7.8 Hz, 1H), 11.02 (bs, 1H). Anal. Calcd for C₁₉H₂₇N₃O₃.HCl: C, 59.75; H, 7.39; Cl, 9.28; N, 11.00. Found: C, 59.98; H, 7.38; 8.96; N, 10.85.

10

Example 104(±)-trans-2-Amino-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide Hydrochloride [(±) 5b HCl]

15 To a solution of (±) 5a HCl (0.5 g, 1.31 nmol) in 30 mL of CH₃OH was added 10% Pd/C (100 mg) and hydrogenated at 50 PSI in a Parr Apparatus at ambient temperature for 3 h. The catalyst was removed by filtration through a celite pad and washed with hot CH₃OH and the combined filtrate was evaporated to dryness. The residue was recrystallized from 2-propanol to give (±) 5b HCl as a white solid, 0.45 g (95%); mp 213-215°C; ¹H NMR(200 MHz, CDCl₃) δ 1.05-1.40 (m, 2H), 1.65-2.25 (m, 8H), 3.10 (s, 3H), 2.90-3.25 (m, 4H), 3.50 (d, J = 12.0, 1H), 3.65 (m, 1H), 3.88 (m, 1H), 4.20 (d, J = 12.5 Hz, 1H), 4.70 (m, 1H), 6.65 (m, 2H), 7.00 (m, 2H), 7.25 (bs, 2H). Anal. Calcd for C₁₉H₂₉N₃O.HCl.0.5H₂O: C, 63.23; H, 8.66; N, 11.64. Found: C, 63.59; H, 8.76; N, 11.61.

20

25

Example 105(±)-trans-2-Nitro-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5c HCl]

30 The compound was prepared according to the literature method (DeCosata, B.; Linda, B.; Rothman, R. B.; Jacobson, A. E.; Bykov, V.; Pert, A.; Rice, K. E. FEBBS Lett. 1989, 249, 178-182); ¹H NMR(200 MHz, CDCl₃) δ 1.15-1.45 (m, 2H), 1.55-2.30 (m, 8H), 3.10 (s, 3H), 2.85-3.20 (m, 4H), 3.40 (m, 1H), 3.88 (m, 1H), 4.25 (d, J = 14.5 Hz, 1H), 4.45 (d, J = 15.0 Hz, 1H),

4.65 (m, 1H), 7.70 (s, 1H), 8.13 (s, 1H). Anal. Calcd for $C_{19}H_{25}Cl_2N_3O_3.HCl$: C, 50.62; H, 5.81; N, 9.32. Found: C, 50.61; H, 5.61; N, 9.20.

Example 106

5 **(±)-trans-2-Amino-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5d HCl]**

Obtained from (±) 5c HCl following the literature procedure (DeCosata, B.; Linda, B.; Rothman, R. B.; Jacobson, A. E.; Bykov, V.; Pert, A.; Rice, K. E. FEBBS Lett. 1989, 249, 178-182); 1H NMR(200 MHz, $CDCl_3$) δ 1.10-1.40 (m, 4H), 1.48-2.20 (m, 8H), 3.00 (s, 3H), 3.10-3.30 (m, 4H), 3.55 (d, J = 14.0 Hz, 1H), 3.85 (d, J = 14.0 Hz, 1H), 4.50 (m, 1H), 6.75 (s, 1H), 7.08 (s, 1H). Anal. Calcd for $C_{19}H_{27}Cl_2N_3O.HCl0.75H_2O$: C, 52.54; H, 6.84; N, 9.67. Found: C, 52.561; H, 6.63; N, 9.33.

15 **Example 107**

(±)-trans-2-Methanesulfonamido-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5e HCl]

To a solution of free base of (±) 5b (1.0 g, 3.2 mmol) in 40 mL of dry CH_2Cl_2 at 0°C under a nitrogen atmosphere was added Et_3N (1.86 g, 18.4 mmol). A solution of methanesulfonyl chloride (1.14 g, 9.92 mmol) in 15 mL of dry CH_2Cl_2 was added dropwise within 15 min. After 2 h at room temperature TLC [solvent system: $CHCl_3:CH_3OH:28\% NH_4OH$ (93:5:2)] showed still starting material was present. Additional amounts of Et_3N (1.86 g) and methanesulfonyl chloride (1.14 g) were added and stirring was continued for another 2 h by this time no starting material was present in the reaction mixture. After the mixture was diluted with 40 mL CH_2Cl_2 of , it was washed with saturated $NaHCO_3$, water, saturated salt solution, and dried over anhydrous Na_2SO_4 . Removal of solvent under reduced pressure gave the bis-sulfoamide as a brown foam which was used directly in the following hydrolysis.

To a solution of bis-sulfonamide (1.0 g, 2.12 mmol) in 60 mL of $CH_3OH:THF$ (2:1) was added 10 M aqueous $NaOH$ (0.96 mL, 9.6 mmol).¹³ The mixture was stirred at room temperature for 30 min and then acidified with 1N HCl. The solvent was evaporated under reduced pressure and the residue was redissolved in CH_2Cl_2 . The CH_2Cl_2 layer was then washed with 5% $NaHCO_3$, saturated salt solution, and dried over anhydrous Na_2SO_4 . Removal of solvent under reduced pressure chromatography on a silica gel column [solvent system: $CH_2Cl_2:CH_3OH:28\% NH_4OH$ (93:5:2)] gave (±) 5e HCl as a white solid.

NH₄OH (95:5:2)] gave the mono-sulfonamide (free base) as an oil; ¹H NMR (200 MHz, CDCl₃) δ 1.05-1.95 (m, 12H), 2.45-2.80 (m, 5H), 2.95 (s, 3H), 3.10 (s, 3H), 3.50 (d, J = 13.8 Hz, 1H), 3.65 (m, 1H), 3.85 (d, J = 14.0 Hz, 1H), 4.45 (m, 1H), 7.05 (m, 1H), 7.15 (m, 2H), 7.45 (d, J = 8.5 Hz, 1H). The hydrochloride salt was prepared by dissolving the free base in CH₂Cl₂ and adding 5 1.2 equivalents of 1M ethereal HCl and recrystallizing from 2-propanol to give (±) 5e HCl as beige colored solid, 0.37 g (38%); mp 229-231°C; ¹H NMR (200 MHz, CDCl₃) δ 1.10-2.20 (m, 12H), 2.90-3.20 (m, 4H), 3.00 (s, 3H), 3.15 (s, 3H), 3.50 (m, 1H), 3.65 (d, J = 13.5 Hz, 2H), 3.80 (m, 1H), 4.40 (m, 1H), 7.05-7.30 (m, 3H), 7.60 (d, J = 8.0 Hz, 1H), 8.90 (bs, 1H). Anal. Calcd for C₂₀H₃₁N₃O₃S.HCl.0.25H₂O: C, 55.28; H, 7.54; N, 9.67. Found: C, 55.40; H, 7.39; N, 9.49.

10

Ref.

(13) Li, C.-S.; Black, W. C.; Chan, C.-C.; Ford-Hutchinson, A. W.; Gauthier, J.-Y.; Gordon, R.; Guay, D.; Kargman, S.; Lau, C. K.; Mancini, J.; Ouimet, N.; Roy, P.; Vickers, P.; Wong, E.; Young, R. N.; Zamboni, R.; Prasit, P. *J. Med. Chem.* **1995**, 38, 4897-4905.

15

Example 108

N-[2-(±)-trans-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride [(±) 5f HCl]

To a stirred solution of (±) 5b (free base, 1.0 g, 3.2 mmol) in 15 mL of dry DMF at room temperature under a nitrogen atmosphere was added 95% NaH (0.083 g, 3.3 mmol). After stirring at room temperature for 30 min, the turbid solution was added to a stirred solution of tert-butyl bromoacetate (0.66 g, 3.4 mmol) in 10 mL of dry DMF. The reaction mixture was continued stirring for 72 h however TLC of the reaction mixture [solvent system: CHCl₃:CH₃OH:28% NH₄OH (93:5:2)] showed still starting material was present. The solvent was removed under reduced pressure and the residue was partitioned between CH₂Cl₂/water. The product was purified on a silica gel column from CH₂Cl₂:CH₃OH (9:1) and was recrystallized from CH₂Cl₂:Et₂O (1:1) to give the corresponding tert-butyl ester, 0.16 (12%); ¹H NMR (200 MHz, CDCl₃) δ 1.05-1.35 (m, 4H), 1.35 (s, 9H), 1.55-2.20 (m, 8H), 2.92 (b, 4H), 3.12 (s, 3H), 3.45 (m, 1H), 3.60 (d, J = 14.0 Hz, 2H), 3.78 (bt, 2H), 3.95 (m, 1H), 5.75 (b, 1H), 6.38 (d, J = 6.5 Hz, 1H), 6.60 (t, J = 5.5 Hz, 1H), 7.00 (m, 2H). The starting material was also recovered in 50% yield.

The tert-butyl ester (0.16 g, 0.372 mmol) was suspended in 10 mL of 4N aqueous HCl and added one drop of anisole and the mixture was stirred at room temperature for 24 h. The

solvent was evaporated under reduced pressure and the residue was redissolved in CH₃CN and filtered. The filtrate was evaporated under reduced pressure and the residue was recrystallized from 2-propanol:ether (1:1) to give (±) 5f HCl as a white solid, 0.070 g (42%); mp 212-214°C (d); ¹H NMR (200 MHz, DMSO-d₆) δ 1.15-2.25 (m, 12H), 2.90 (m, 1H), 3.05 (s, 3H), 3.14-3.70 (m, 6H), 3.85 (bs, 2H), 4.55 (b, 1H), 6.37 (d, J = 6.0 Hz, 1H), 6.55 (t, J = 5.0 Hz, 1H), 6.95 (m, 2H), 9.80 (b, 1H). Anal. Calcd for C₂₁H₃₁N₃O₃.HCl.H₂O: C, 58.93; H, 8.00; N, 9.81. Found: C, 58.79; H, 7.64; N, 9.43.

Example 109

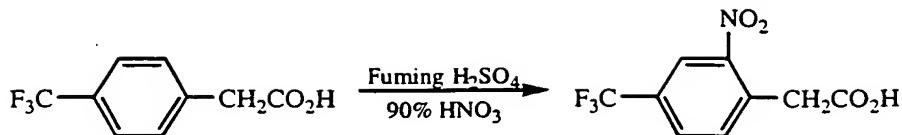
10 (±)-trans-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide
Hydrochloride [(±) 5g HCl]

To a solution of 4-trifluoromethylphenyl acetic acid (1.45 g, 7.08 mmol) in 10 mL of dry CH₂Cl₂ under a nitrogen atmosphere was added 1-hydroxybenzotriazole hydrate (HOBT) (0.95 g, 7.08 mmol) and stirred. The reaction mixture was cooled to 0→ 5°C and added solid EDCI ([1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide HCl])(1.35 g, 7.08 mmol) and stirrat this temperature for 30 min. A solution (±) 3 (1.0 g, 5.48 mmol) in 10 mL of dry CH₂Cl₂ was added followed by N,N-diisopropylethylamine (Hunig's Base) (0.915 g, 7.08 mmol). The reaction mixture was stirred for 24 h while warming to the room temperature. The reaction mixture was then poured on to excess of ice-cold saturated aqueous NaHCO₃ solution and stirred for 30 min. After dilution with CH₂Cl₂, the organic was separated, washed with saturated salt solution, and dried over anhydrous Na₂SO₄. Removal of solvent gave a brown oil which was chromatogrphed on a silica gel column [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (99:1:2)] to give the desired product as free base. The hydrochloride salt was prepared from 1M etherial HCl and recrystallized from CH₂Cl₂: Et₂O (1:1) to give (±) 5g HCl as a cream colored solid, 0.68 g (30%); 213-215°C; ¹H NMR (200 MHz, CDCl₃) δ 1.02-1.47 (m, 4H), 1.52-2.22 (m, 8H), 2.75-2.90 (m, 2H), 2.94 (s, 3H), 3.07 (m, 1H), 3.37 (m, 1H), 3.62 (d, J = 15.0 Hz, 1H), 3.77 (m, 1H), 4.17 (d, J = 15.0 Hz, 1H), 4.57 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H). Anal. Calcd for C₂₀H₂₇F₃N₂O.HCl.0.25H₂O: C, 58.68; H, 7.02; N, 6.84. Found: C, 58.68; H, 6.84; N, 6.69.

30

Nitration of 4-trifluoromethylphenyl acetic acid :

General procedure:



5 **Preparation of 2-nitro-4-trifluoromethylphenyl acetic acid [4, R = 2-NO₂(4-CF₃) -C₆H₄CH₂]**

To a solution of 4-trifluoromethylphenyl acetic acid (2.5 g, 12.25 mmol) in 8 mL of glacial acetic acid at 0°C under an anhydrous atmosphere was added 5 mL of fuming H₂SO₄ (11% SO₃) (caution !) followed by cautious addition of 90% HNO₃ (3.5 mL, 73.14 mmol) within 10 min. The reaction mixture was then stirred at room temperature for 2 h and poured into ice-water. The resulting solid was filtered and washed with cold deionized water to give the desired product after drying as off-white solid, 2.5 g (82%); ¹H NMR (200 MHz, CDCl₃) δ 4.02 (s, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.74 (d, J = 8.0 Hz, 2H), 8.28 (s, 1H). The product was used directly into the following reactions.

15

Example 110

(±)-trans-2-Nitro-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5h HCl]

20 Prepared from 2-nitro-4-trifluoromethylphenyl acetic acid following the procedure described in Example II to give (±) 5h HCl as cream colored solid in 56% yield; mp 259-261°C (d); ¹H NMR (200 MHz, CDCl₃) δ 1.10-1.42 (m, 4H), 1.51-2.25 (m, 8H), 2.95-3.25 (m, 3H), 3.14 (s, 3H), 3.40 (m, 1H), 3.90 (m, 1H), 4.35 (d, J = 13.8 Hz, 1H), 4.55 (d, J = 14.0 Hz, 1H), 4.60 (m, 1H), 7.80 (dd, J = 7.8 Hz, 2H), 8.25 (s, 1H). Anal. Calcd for C₂₀H₂₆F₃N₃O₃·HCl·0.25H₂O: C, 52.86; H, 6.10; N, 9.25. Found: C, 52.85; H, 6.02; N, 9.13.

Example 111

(±)-trans-2-Amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5i HCl]

30

To a solution of free base 4h (0.4 g, 0.97 mmol) in 20 mL of absolute alcohol was added 2 ml of hydrazine hydrate and the reaction mixture was stirred at 50°C under a nitrogen

atmosphere. Raney® nickel (50% slurry in water) was added slowly and the progress of the reaction was monitored on TLC plate [solvent system: CHCl₃: CH₃OH: 28% NH₄OH (99:1:2)]. If needed more of the Raney® nickel was added to the reaction mixture. When reaction was completed, excess of Raney® nickel was introduced to decompose the hydrazine hydrate. The 5 reaction mixture was filtered through a celite pad and the pad was washed with hot CH₃OH. The filtrate was evaporated to dryness. The residue was purified on a silica gel column [solvent system: CHCl₃: CH₃OH: 28% NH₄OH (99:1:2)] and the hydrochloride salt was prepared from 1M etherial HCl. Recrystallization from CH₂Cl₂:Et₂O (2:1) gave (±) 5i HCl as a white solid, 0.2 g (48%); mp 248-250°C (d); ¹H NMR (200 MHz, DMSO-d₆) δ 1.15 -2.18 (m, 12H), 3.00 (s, 3H), 10.0 (bs, 1H). Anal. Calcd for C₂₀H₂₈F₃N₃O.HCl.0.5H₂O: C, 56.01; H, 7.05; N, 9.80. Found: C, 55.70; H, 7.03; N, 9.65.

15 **Example 112**

(±)-trans-2-Bismethanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide [(±) 5j HCl]

The compound was prepared from free base (±) 5i (0.5 g, 1.30 mmol) following the procedure described in the first part of the preparation of (±) 5e. The bismethanesulfonamide was 20 purified on a silica gel column [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (96:2:2)] to give the desired product as a foam. The hydrochloride salt was prepared from 1M etherial HCl and recrystallized from 2-propanol:Et₂O (1:1) to give (±) 5j HCl as a beige colored solid, 0.23 g (30%); mp 224-226°C (d); ¹H NMR (200 MHz, CDCl₃) δ 1.12-1.51 (m, 4H), 1.53-2.24 (m, 8H), 1.82-3.17 (m, 2H), 2.98 (s, 3H), 3.32-3.56 (m, 2H), 3.28 (s, 3H), 3.33 (s, 3H), 3.77 (m, 1H), 3.97 25 (d, J = 14.0 Hz, 1H), 4.27 (d, J = 14.0 Hz, 1H), 4.62 (m, 1H), 7.39 (s, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H). Anal. Calcd for C₂₂H₃₂F₃N₃O₅S₂.HCl: C, 45.87; H, 5.77; N, 7.29. Found: C, 45.53; H, 5.81; N, 7.00.

Example 113(\pm)-*trans*-2-Methanesulfonamido-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(\pm) 5k HCl]

5 To a solution of (\pm) 5j HCl (0.16 g, 0.23 mmol) in 9 mL of CH₃OH:THF (2:1) at room temperature was added 0.12 mL of 10M aqueous NaOH and the mixture was stirred for 30 min. The reaction mixture was neutralized with 1N HCl and evaporated to dryness. The residue was redissolved in CH₂Cl₂ and basified with saturated aqueous solution of NaHCO₃. The organic layer was separated, washed with water, saturated salt solution, and dried over anhydrous 10 Na₂SO₄. Removal of solvent under reduced pressure gave the product as a free base. The hydrochloride salt was prepared from 1M etherial HCl and recrystallized from CH₂Cl₂: Et₂O (1:1) to give (\pm) 5k HCl as a beige colored solid, 0.085 g (61%); 209-211°C (d); ¹H NMR (200 MHz, CDCl₃) δ 1.15-1.24 (m, 4H), 1.50-2.10 (m, 8H), 2.20 (m, 2H), 2.90-3.10 (m, 2H), 3.05 (s, 6H), 3.55 (m, 2H), 3.80 (m, 1H), 4.64 (m, 1H), 7.20 (dd, J = 7.8 Hz, 2H), 7.88 (s, 1H), 9.00 (s, 1H). Anal. Calcd for C₂₁H₃₀F₃N₃O₃S.HCl.0.125 H₂O: C, 50.42; H, 6.30; N, 8.40. Found: C, 15 50.62; H, 6.49; N, 8.00.

Example 114N-[2-(\pm)-*trans*-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride [(\pm) 5l HCl]

20 To a solution of free base (\pm) 5i (0.767, 2.0 mmol) in 10 mL of anhydrous THF under a nitrogen atmosphere at 0°C was added N,N-diisopropylethylamine (Hunig's Base) (1.55 g, 12.0 mmol). The reaction mixture was stirred at 0°C for 15 min then added bromoacetic acid t-butyl ester (1.95 g, 10.0 mmol) and the reaction mixture was continued to stir while warming to room 25 temperature 72 h. The solvent was evaporated at reduced pressure and the residue was partitioned between CH₂Cl₂ and water. The organic layer was then washed with, saturated NaHCO₃, saturated salt solution, and dried over anhydrous Na₂SO₄. Removal of solvent gave the crude product which was purified on a silica gel column [solvent system: CHCl₃: CH₃OH: 28% 30 NH₄OH (96:2:2)] to give the intermediate t-butyl ester 0.477 g (40%); ¹H NMR (200 MHz, CDCl₃) δ 1.05-1.25 (m, 4H), 1.38-1.90 (m, 8H), 1.40 (s, 9H), 2.15-2.75 (m, 5H), 2.85 (s, 3H), 3.60 (m, 2H), 3.75 (d, J = 4.0 Hz, 2H), 4.45 (m, 1H), 5.85 (m, 1H), 6.55 (s, 1H), 6.80 (d, J = 7.5 Hz, 1H), 7.10 (d, J = 7.8 Hz, 1H).

The above t-butyl ester (0.47 g, 0.77 mmol) was suspended in 10 mL of aqueous 4N HCl and added 2-3 drops of anisole. The reaction mixture was stirred at room temperature for 72 h and filtered. The filtrate was evaporated to dryness, redissolved in CH₃CN, filtered again, and concentrated. Addition of the ether gave the product which was filtered, washed with ether, and dried to give (±) 5l HCl as a beige colored solid, 0.17 g (41%); mp 178-180°C (d); MS (FAB) 442 (M+1); ¹H NMR (200 MHz, CDCl₃) δ 1.05-2.20 (m, 12H), 2.75 (s, 3H), 2.90-3.25 (m, 5H), 3.30-3.55 (m, 2H), 3.70-4.35(m, 4H), 4.65 (m, 1H), 6.72 (s, 1H), 6.80 (m, 1H), 6.95 (d, J = 7.7 Hz, 1H). Anal. Calcd for C₂₂H₃₀F₃N₃O₃.HCl.0.125Et₂O: C, 55.47; H, 6.67; N, 8.62. Found: C, 55.64; H, 7.06; N, 9.00.

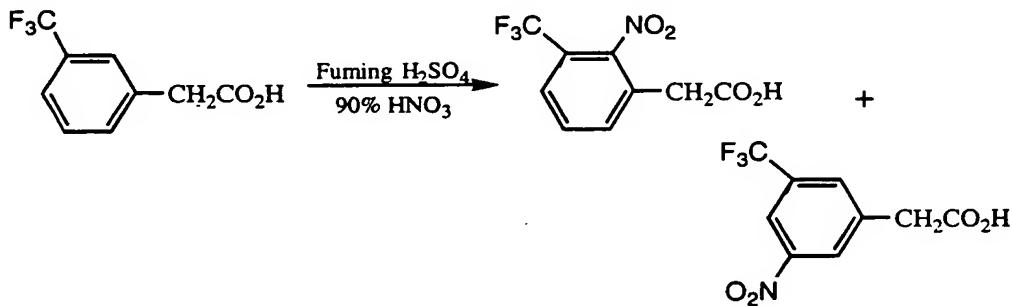
10

Example 115

(±)-trans-3-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5m HCl]

15 Following the Example II, (±) 5m HCl was prepared from 3-trifluoromethylphenyl acetic acid in 67% yield as a cream colored solid; mp 245-247°C; ¹H NMR (200 MHz, CDCl₃) δ 1.15-1.55 (m, 4H), 1.60-2.30 (m, 8H), 2.80-3.05 (m, 2H), 3.00 (s, 3H), 3.18 (m, 1H), 3.45 (m, 1H), 3.75 (d, J = 15.0 Hz, 1H), 3.85 (m, 1H), 4.25 (d, J = 14.8 Hz, 1H), 4.65 (m, 1H), 7.40 (m, 4H). Anal. Calcd for C₂₀H₂₇F₃N₂O.HCl.0.25H₂O: C, 58.68; H, 7.02; N, 6.84. Found: C, 58.46; H, 7.17; N, 6.69.

Nitration of 3-trifluoromethylphenyl acetic acid :



25

Preparation of 2-nitro-3-trifluoromethylphenyl acetic acid [4, R = 2-NO₂(3-CF₃) - C₆H₄CO₂H] and preparation of 5-nitro-3-trifluoromethylphenyl acetic acid [4, R = 5-NO₂(3-CF₃) - C₆H₄CO₂H]

5 The nitration of 3-trifluorophenylacetic acid as shown earlier resulted into a 1:1 non-separable mixture of 2- and 5-nitro compounds in 66% yield. The structural assignment of the compounds were made on the basis of ¹H NMR spectrum. The mixture was used in the condensation reaction.

10 Example 116

(±)-trans-5-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5n HCl] and (±)-trans-2-Nitro-3-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5o HCl]

15 The compounds were prepared as shown in Example 109 and the mixture of 2- and 5-nitrophenylacetic acids to give the mixture of products. Initially the compounds were separated on a silica gel column [solvent system: CHCl₃: CH₃OH: 28% NH₄OH (96:2:2)] which resulted in the free base of the compounds as pure mixture. The products were again purified on Chromatotran using a 4 mm silica gel plate [solvent system: CHCl₃ containing 2% NH₄OH]. The 20 first product was isolated and converted to the hydrochloride salt and the salt was recrystallized from 2-propanol:ether (1:1) to give (±) 5n HCl as a cream colored solid in 10% yield; mp 236-238°C; ¹H NMR (200 MHz, CDCl₃) δ 1.15-1.55 (m, 4H), 1.65-2.30 (m, 8H), 2.85-3.20 (m, 3H), 3.10 (s, 3H), 3.40 (m, 1H), 3.70 (d, J = 14.0 Hz, 1H), 3.85 (m, 1H), 4.60 (brd, 2H), 7.90 (s, 1H), 8.25 (s, 1H), 8.32 (s, 1H). Anal. Calcd for C₂₀H₂₆F₃N₃O₃.HCl: C, 53.39; H, 6.05; N, 9.34. Found: 25 C, 53.28; H, 6.06; N, 9.36.

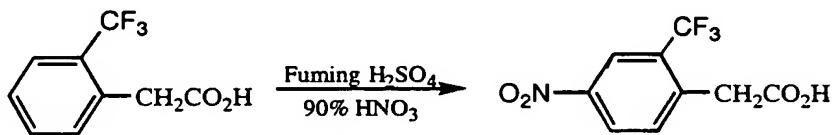
25 The second product, (±) 5o HCl, was also isolated in 10% yield after the recrystallization of the hydrochloride salt from 2-propanol:ether (1:1) as a white solid; mp 243-245°C (d); ¹H NMR (200 MHz, CDCl₃) δ 1.10-1.50 (m, 4H), 1.55-2.20 (m, 8H), 2.90-3.20 (m, 3H), 3.10 (s, 3H), 3.44 (m, 1H), 3.65 (d, J = 13.5 Hz, 1H), 3.90 (m, 1H), 4.65 (brd, 2H), 7.70 (s, 1H), 7.82 (s, 2H). Anal. Calcd for C₂₀H₂₆F₃N₃O₃.HCl.H₂O: C, 51.34; H, 6.25; N, 8.98. Found: C, 51.69; H, 6.24; N, 8.89.

Example 117(±)-trans-2-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5p HCl]

5 The compound was prepared from 2-trifluoromethylphenylacetic acid following the Example II. The hydrochloride salt was made from 1M etherial HCl and recrystallized from 2-propanol:ether (1:1) to give (±) 5p HCl in 20% yield as a white solid; mp 282-284°C (d); ¹H NMR (200 MHz, CDCl₃) δ 1.20-1.50 (m, 4H), 1.55-2.30 (m, 8H), 3.85-3.04 (m, 2H), 3.08 (s, 3H), 3.10-3.27 (m, 1H), 3.40-3.60 (m, 1H), 3.90 (m, d, J = 14.5 Hz, 2H), 4.26 (d, J = 14.7 Hz, 1H), 4.63 (m, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 2H).
 10 Anal. Calcd for C₂₀H₂₇F₃N₂O.HCl: C, 59.33; H, 6.97; N, 6.92. Found: C, 59.28; H, 6.73; N, 6.84.

Nitration of 2-trifluoromethylphenyl acetic acid :

15

Preparation of 4-nitro-2-trifluoromethylphenyl acetic acid [4, R = 4-NO₂(2-CF₃) - C₆H₄CO₂H]

20

The nitration of 2-trifluorophenylacetic acid as depicted in Scheme III gave mostly the corresponding 4-nitro derivative and only a trace amount of 6-nitro compound was detected in the proton NMR; ¹H NMR (200 MHz, CDCl₃) δ 3.90 (s, 2H), 7.55 (d, J = 8.4 Hz, 1H), 8.35 (dd, J = 2.4, 8.0 Hz, 1H), 8.50 (d, J = 2.4 Hz, 1H). The compound was used directly into the following 25 coupling reaction.

Example 118(±)-trans-4-Nitro-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [(±) 5q HCl]

30

The compound was prepared following the coupling method described in Example 109 from 4-nitro-2-trifluorophenylacetic acid. The hydrochloride salt was prepared by known method and recrystallized from 2-propanol:ether (1:1) to give (±) 5q HCl as a beige colored solid in 37%

yield; mp 265-267°C (d); ^1H NMR (200 MHz, CDCl_3) δ 1.15-1.45 (m, 4H), 1.50-2.30 (m, 8H), 2.85-3.20 (m, 3H), 3.05 (s, 3H), 3.45 (m, 1H), 3.90 (m, d, J = 14.0 Hz, 2H), 4.60 (brd, 2H), 8.00 (d, J = 8.0 Hz, 1H), 8.25 (dd, J = 2.4, 8.0 Hz, 1H), 8.40 (d, J = 2.4 Hz, 1H). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{F}_3\text{N}_3\text{O}_3\text{HCl}$: C, 53.39; H, 6.05; N, 9.34. Found: C, 53.29; H, 5.93; N, 9.17.

5

Example 119

(\pm)-trans-4-Amino-2-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide Hydrochloride [\pm 5r 2HCl]

10 The compound was prepared from free base (\pm) 5q following the reduction procedure described for the preparation of (\pm) 5h. The free base was converted to di-hydrochloride from 1M etherial HCl and recrystallized from $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}:\text{Et}_2\text{O}$ (6:3:1) to give (\pm) 5r 2HCl as a white solid in 68% yield; mp 288-290°C (d); ^1H NMR (200 MHz, DMSO-d_6) δ 1.10-2.20 (m, 12H), 2.98 (s, 3H), 3.00-3.30 (m, 4H), 3.50 (m, 1H), 3.80 (d, J = 14.5 Hz, 1H), 4.20 (d, J = 14.8 Hz, 1H), 4.50 (m, 1H), 7.50 (m, 3H). Anal. Calcd for $\text{C}_{20}\text{H}_{28}\text{F}_3\text{N}_3\text{O}.2\text{HCl}$: C, 52.64; H, 6.63; N, 9.21. Found: C, 52.67; H, 6.52; N, 9.06.

Example 120

(\pm)-trans-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]2,2-dphenylacetamide Hydrochloride [\pm 5s HCl]

20 The compound was prepared from diphenylacetic acid following the general procedure for the preparation of aryl acetamides. The hydrochloride salt was recrystallized from 2-propanol to give (\pm) 5s HCl as a white solid in 20% yield; mp 295-297°C (d); ^1H NMR (200 MHz, CDCl_3) δ 1.20-2.40 (m, 12H), 2.85-3.15 (m, 2H), 3.00 (s, 3H), 3.25-3.60 (m, 2H), 3.95 (m, 1H), 4.75 (m, 1H), 5.70 (s, 1H), 7.35 (m, 10H). Anal. Calcd for $\text{C}_{25}\text{H}_{32}\text{N}_2\text{O}.\text{HCl}.0.25\text{H}_2\text{O}$: C, 71.92; H, 8.09; N, 6.71. Found: C, 72.25; H, 8.40; N, 6.52.

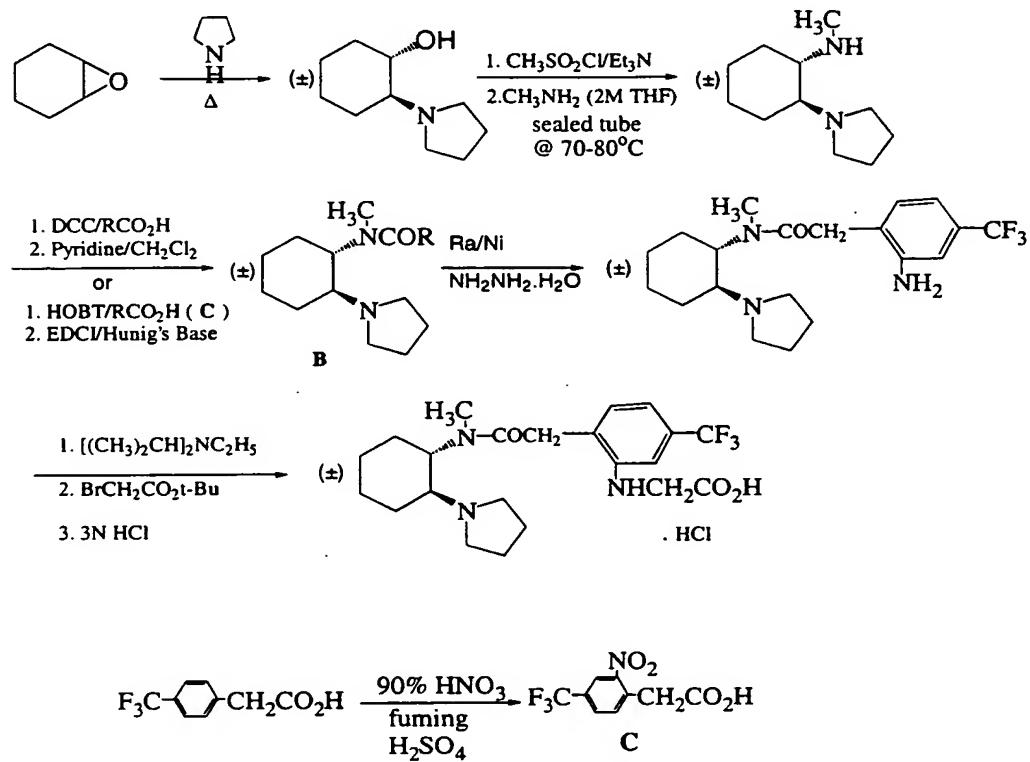
Example 121

(\pm)-trans-4-Methylsulfonyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide Hydrochloride [\pm 5t HCl]

30 The compound was prepared from 4-methylsulfonylphenylacetic acid to the method of Example 109 and the hydrochloride salt was recrystallized from $\text{CH}_2\text{Cl}_2:\text{ET}_2\text{O}$ (1:1) to give (\pm) 5t

HCl as a cream colored solid in 50% yield; mp 152-154°C (d); ^1H NMR (200 MHz, CDCl_3) δ 1.10-2.30 (m, 12H), 2.95 (s, 6H), 3.00-3.25 (m, 2H), 3.40 (m, 1H), 3.65 (d, J = 14.5 Hz, 1H), 3.85 (m, 1H), 4.35 (d, J = 14.0 Hz, 1H), 4.67 (m, 1H), 7.45 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0

Scheme O



Hz, 2H). Anal. Calcd for $\text{C}_{20}\text{H}_{30}\text{N}_2\text{O}_3\text{S} \cdot \text{HCl} \cdot 1.5\text{H}_2\text{O}$: C, 54.35; H, 7.75; N, 6.34. Found: C, 54.20; H, 7.38; N, 6.15.

Preparation of compounds 4a through 4l of formula IVA is according to Scheme O.

The chiral compounds were prepared from the enantiomeric pure diamine **B**.

Example 4a

10 (Z)-4-[2-((±)-trans-2-Amino-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]phenylacetamido)4-oxo-2-butenoic acid

To a solution of (\pm) -trans-2-amino-4,5-dichloro-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide3 (0.12 g, 0.312 mmol) in anhydrous THF (2.5 mL) under anitrogen atmosphere was added maleic anhydride (0.03 g, 0.312 mmol). The reaction

mixture was stirred at room temperature for 3 days. The precipitated solid was filtered off, washed with anhydrous THF, and dried to give **4a** (0.088 g, 58%); mp 246-248°C (d); MS (FAB) 482 (M⁺). Anal. Calcd. for C₂₃H₂₉Cl₂N₃O₄.H₂O: C, 55.20; H, 6.24; N, 8.40. Found: C, 55.32; H, 6.01; N, 8.09.

5 Ref.

3. de Costa, B. R. et. al. FEBS Lett. 249, 178-182 (1989).

Example 4b

(Z)-4-[2-((±)-trans-2-Amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]-phenylaetamido]4-oxo-2-butenoic acid

10 The compound **4b** was prepared from (±)-trans-2-amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)-cyclohexyl]phenylaetamide¹ following the above procedure in 60% yield; mp 256-258°C; ¹H NMR (300 MHz, DMSO-d₆) δ 1.15 -2.18 (m, 12H), 3.01 (s, 3H), 3.15-4.10 (m, 15 7H), 4.50 (m, 1H), 5.95 (d, J = 15.0 Hz, 1H), 6.35 (d, J = 14.5 Hz, 1H), 7.37 (m, 2H), 8.16 (s, 1H). Anal. Calcd for C₂₄H₃₀F₃N₃O₄: C, 59.87; H, 6.28; N, 8.37. Found: C, 59.64; H, 6.14; N, 8.57.

Example 4c

(±)-trans-2-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-pyridylacetamide dihydrochloride

20 The compound **4c** was prepared from 2-pyridyl acetic acid hydrochloride and (±)-trans-2-pyrrolidinyl-N-methylcyclohexylamine³ following the general procedure in 37% yield; mp 264-266°C (d); ¹H NMR (300 MHz, DMSO-d₆) δ 1.10 -2.00 (m, 12H), 3.04 (s, 3H), 3.15-4.70 (m, 25 5H), 4.30 (d, J = 16 Hz, 1), 4.55 (m, 1H), 4.67 (d, J = 16.0 Hz, 1H), 7.82 (t, J = 7.5 Hz, 1H), 8.10 (d, J = 7.8 Hz, 1H), 8.55 (t, J = 7.5 Hz, 1H), 8.88 (d, J = 7.0 Hz, 1H). Anal. Calcd for C₁₈H₂₇N₃O.2HCl.0.25H₂O: C, 57.07; H, 7.85; N, 11.09. Found: C, 57.04; H, 7.48; N, 10.69.

Example 4d

(±)-trans-3-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-5-bromo-pyridylacetamide hydrochloride

30 The compound **4d** was prepared 5-bromo-3-pyridyl acetic acid in 77% yield; mp 130-132°C; ¹H NMR (free base 200 MHz, CDCl₃) δ 1.00 -2.00 (m, 12H), 2.88 (s, 3H), 2.35-2.77 (m,

5H), 3.75 (m, 2H), 4.50 (m, 1H), 7.65 (bs, 1H), 8.30 (bs, 1H), 8.67(s, 1H). Anal. Calcd for C₁₈H₂₆BrN₃O.HCl: C, 51.87; H, 6.53; N, 10.08. Found: C, 51.48; H, 6.11; N, 9.70.

5 **Example 4e**

(\pm)-trans-3,5-Di-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide hydrochloride

Prepared from 3,5-di-trifluoromethyl-phenyl acetic acid in 27% yield; mp 211-213°C; ¹H NMR (300 MHz, CDCl₃) δ 1.20 -2.25 (m, 12H), 3.04 (s, 3H), 3.00-3.35 (m, 3H), 3.50 (m, 1H), 3.80 (d, J = 15.0 Hz, 1H), 4.00 (m, 1H), 4.60 (m, 2H), 7.75 (s, 1H), 7.84 (s, 2H). Anal. Calcd for C₂₁H₂₆F₆N₂O.HCl: C, 53.34; H, 5.75; N, 5.92. Found: C, 53.14; H, 5.74; N, 5.76.

15 **Example 4f**

(\pm)-trans-3-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-(trans-3-furyl)acetamide hydrochloride

The compound 4f was prepared from trans-3-furan acrylic acid in 56% yield; mp 164-166°C (d); ¹H NMR (200 MHz, CDCl₃) δ 1.20 -2.25 (m, 12H), 3.15(s, 3H), 2.75-3.95 (m, 4H), 4.70 (m, 2H), 6.57 (bs, 1H), 6.65 (d, J = 15.0 Hz, 1H), 7.34 (s, 1H), 7.46 (d, J = 15.2 Hz, 1H), 7.55 (s, 1H). Anal. Calcd for C₁₈H₂₆N₂O₃.HCl.0.5H₂O: C, 62.15; H, 8.11; N, 8.05. Found: C, 61.94; H, 8.01; N, 7.91.

25 **Example 4g**

(\pm)-trans-2-Methoxy-3-methylsulfamoyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide hydrochloride

The compound 4g was prepared from 2-methoxy-3-methylsulfamoyl-phenyl acetic acid (prepared from methyl 2-methoxy phenyl acetic acid by the procedure reported earlier) in 45% yield; mp 168-170°C; ¹H NMR (200 MHz, CDCl₃) δ 1.15 -2.20 (m, 12H), 2.52 (d, J = 2.5 Hz, 3H), 2.76 (s, 3H), 2.40-2.70 (m, 4H), 3.58 (d, J = 5.0 Hz, 1H), 3.79 (s, 3H), 3.84 (d, J = 4.8 Hz, 1H), 4.75 (m, 2H), 6.84 (d, J = 8.7 Hz, 1H), 7.65 (m, 2H). Anal. Calcd for C₂₁H₃₃N₃O₄S.HCl.0.5H₂O: C, 53.78; H, 7.52; N, 8.96. Found: C, 53.80; H, 7.50; N, 8.90.

Example 4h**(±)-trans-3-N-Methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]indoleacetamide hydrochloride**

Prepared from indole 3-acetic acid in 61% yield; 262-264°C; ^1H NMR (300 MHz,

DMSO-d₆) δ 1.20 -2.15 (m, 12H), 2.95 (s, 3H), 2.97-3.55 (m, 4H), 3.83 (s, 2H), 4.55 (m, 2H), 6.96 (t, J = 7.5 Hz, 1H), 7.02 (t, J = 7.0 Hz, 1H), 7.17 (s, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H). Anal. Calcd for C₂₁H₂₉N₃O.0.9HCl: C, 67.75; H, 8.10; N, 11.29. Found: C, 67.78; H, 8.12; N, 11.22.

Example 4i**(±)-trans-4-Fluoro-3-methylsulfamoyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenylacetamide hydrochloride**

The compound **4i** was prepared from 4-fluoro-3-methylsulfamoyl phenyl acetic acid in

48% yield; mp 265-267°C; ^1H NMR (200 MHz, DMSO-d₆) δ 1.30 -2.20 (m, 12H), 2.60 (s, 3H), 3.06 (s, 3H), 3.15-3.80 (m, 4H), 3.91 (d, J = 15.0 Hz, 1H), 4.20 (d, J = 15.5 Hz, 1H), 4.65 (m, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.75 (m, 2H). Anal. Calcd for C₂₀H₃₀FN₃O₃S.HCl.H₂O: C, 51.55; H, 7.14; N, 9.02. Found: C, 51.93; H, 6.81; N, 8.70.

Example 4j**N-[1S, 2S-trans-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride**

1S, 2S-trans-2-Nitro-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamide hydrochloride

To a solution of (*1S, 2S*)-(+)-*trans*-2-pyrrolidinyl-N-methylcyclohexylamine³ (1.9 g,

10.42 mmol) in anhydrous CH₂Cl (25 mL) under a nitrogen atmosphere was added 2-nitro-4-trifluorophenyl acetic acid¹ (3.9 g, 15.63 mmol) and pyridine (0.42 mL, 5.21 mmol). The reaction mixture was cooled to 0°C and added DCC (4.3 g, 20.84 mmol) in one portion and stirred the mixture for 3.5 h. The TLC [solvent system: CH₂Cl₂: CH₃OH: 28% NH₄OH (95:5:2)] showed no starting material was present. The DCU was removed by filtration and the solvent was removed under reduced pressure. The residue was partitioned between 10% citric acid (100 mL) and ether (100 mL). The ether layer was discarded and the aqueous layer was washed with ether twice. The aqueous layer was then made alkaline from 28% ammonia hydroxide and the product was extracted with CH₂Cl₂. The organic layer was separated, dried over anhydrous Na₂SO₄, and evaporated to dryness to give the crude product. The hydrochloride salt was prepared from 1M ethereal HCl and recrystallized from 2-propanol:ether (1:1) to give the desired product, 4.2 g

(97%); $[\alpha]^{18.8}_{589} -20.42^\circ$ (c 1.01, CH_3OH); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.20 -2.35 (m, 12H), 2.98-3.28 (m, 4H), 3.20 (s, 3H), 3.45 (m, 1H), 3.98 (m, 1H), 4.45 (d, $J = 14.0$ Hz, 1H), 4.70 (d, $J = 14.5$ Hz, 1H), 7.80 (d, $J = 8.7$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 8.34 (s, 1H). The compound was used directly into the following reaction.

5

1S, 2S-trans-2-Amino-4-trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]phenyl-acetamide hydrochloride

The above 2-nitro compound as hydrochloride salt (4.1 g, 9.09 mmol) was dissolved in methanol (30 mL), added PtO_2 (0.4 g), and hydrogenated at room temperature at atmospheric pressure for 1 h. The catalyst was filtered off, washed with hot methanol and the combined filtrate was evaporated to dryness. The residue was re-crystallized from ethyl acetate to give the 2-amino compound as hydrochloride salt, 3.2 g (84%); $[\alpha]^{18.6}_{589} -6.48^\circ$ (free base, c 0.51, CH_3OH); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.25 -2.35 (m, 12H), 3.00-3.30 (m, 4H), 3.15 (s, 3H), 3.45 (m, 1H), 3.97 (m, 1H), 4.35 (m, 1H), 4.80 (m, 1H), 6.90 (s, d, 2H), 7.05 (d, $J = 7.5$ Hz, 1H). 15 The free base of the 2-amino compound was used to prepare the target compound.

The 2-amino compound (free base, 2.8 g, 7.30 mmol) was dissolved in anhydrous THF (20 mL) under a nitrogen atmosphere. N,N-Diisopropylethylamine (1.88 g, 14.60 mmol) was added at room temperature followed by t-butyl bromoacetate (2.14 g, 11.0 mmol) and the reaction mixture was stirred at room temperature for 3 days. The TLC [solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (95:5:2)] showed still starting material was present, the reaction mixture was heated to 60-70°C (oil-bath temperature) for 48 h after the addition of N,N-diisopropylethylamine (1.88 g, 14.60 mmol) and by t-butyl bromoacetate (2.14 g, 11.0 mmol). The reaction mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was then re-dissolved in CH_2Cl_2 , washed with water, 10% aqueous NaHCO_3 , saturated salt 25 solution, and dried over anhydrous Na_2SO_4 . Removal of solvent at reduced pressure resulted the crude product which was purified on a silica gel column [solvent system: CH_2Cl_2 : CH_3OH : 28% NH_4OH (98:2:2)] to the desired t-butyl ester, 2.3 g (63%), as a foam; %); $[\alpha]^{19.5}_{589} -9.5^\circ$ (c 1.0, CH_2Cl_2); the chiral purity (>90%) of the compound was checked on ChiralPak® AD column; MS (FAB) 498 (M+1); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 1.10-2.00 (m, s, 21H), 2.45-2.75 (m, 4H), 2.90 30 (s, 3H), 3.70 (m, 2H), 3.88 (m, 2H), 4.50 (m, 1H), 6.65 (s, 1H), 6.90 (d, $J = 7.0$ Hz, 1H), 7.20 (d, $J = 7.5$ Hz, 1H).

The t-butyl ester (2.1 g, 4.22 mmol) was dissolved in acetic acid (20 mL) and added 4N aqueous HCl (25 mL). After addition of 4 drops of p-anisole, the reaction mixture was stirred at room temperature for 4 days. The solvent was removed under reduced pressure and the residue was re-dissolved in minimum amount of acetonitrile and added excess of ether. The resulting 5 solid was filtered, washed with ether, and dried. Re-crystallization from acetonitrile:ethylacetate (1:1) gave compound **4j** (1.0 g, 50%); mp 176-178°C; $[\alpha]^{20.5}_{589} +6.5^\circ$ (c 0.5, CH_2Cl_2); ^1H NMR (300 MHz, DMSO- d_6) δ 1.10-2.05 (m, s, 12H), 2.70 (s, 3H), 2.98-3.30 (m, 4H), 3.40-4.15 (m, 6H), 6.65 (s, 1H), 6.82 (d, $J = 7.5$ Hz, 1H), 7.10 (d, $J = 7.5$ Hz, 1H). Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{FN}_3\text{O}_3\text{HCl}$: C, 55.29; H, 6.54; N, 8.79. Found: C, 55.61; H, 6.76; N, 8.97.

10

Example 4k

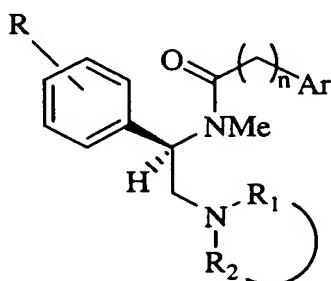
N-[1R, 2R-trans-4-Trifluoromethyl-N-methyl-N-[2-(1-pyrrolidinyl)cyclohexyl]-phenylacetamido]glycine Hydrochloride

The compound was prepared from (1R, 2R)-(-)-trans-2-pyrrolidinyl-N-methylcyclohexyl-15 amine³ (1.9 g, 10.42 mmol) following the above procedures in 36% yield; $[\alpha]^{20.5}_{589} -7.4^\circ$ (c 0.52, CH_2Cl_2). Anal. Calcd for $\text{C}_{22}\text{H}_{30}\text{FN}_3\text{O}_3\text{HCl} \cdot 0.25 \text{CH}_3\text{CN}$: C, 55.35; H, 6.55; N, 9.32. Found: C, 55.78; H, 6.81; N, 9.24.

20

Compounds of Formula IIIB

The following is a description of compounds of formula (IIIB) in accordance with an embodiment of the present invention. In this regard, as noted above, in one aspect of the invention, there are provided compounds of formula (IIIB) which have the following structure:



25

(IIIB)

wherein:

n is an integer from 1 to 3;

R₁ and R₂ are together alkylene of about 4 to about 8 carbons, optionally substituted with a group R', where R' is selected from -OH, halogen, -NR_aR_b, in which R_a and R_b are independently selected from hydrogen, -C(=O)R_c, -SO₂R_d and -C(=O)(CH₂)_mCO₂R_e, in which R_c and R_d are independently selected from alkyl, aryl and heteroaryl, R_e is hydrogen or alkyl and m is an integer from 1 to 3;

Ar is unsubstituted phenyl or mono-, di-, tri-, or tetra-substituted phenyl, wherein said substituents are independently selected from halogen; alkyl; alkoxy; aryloxy; aralkyloxy; alkylene dioxide; -OH; -SO₂R_f in which R_f is alkyl or aryl; -CN; haloalkyl; -NR_gR_h, in which R_g and R_h are independently selected from hydrogen, alkyl, -C(=O)R_f, -C(=O)-N(R_e)₂, -S(O)₂R_f, and -(CH₂)_y-CO₂R_e in which y is an integer from 1 to 3; -S(O)₂N(R_i)(R_j), in which R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with -CO₂R_e, aryl and aralkyl; or R_i and R_j together form -(CH₂)₂X(CH₂)₂-, where X is a direct bond, -CH₂-, -NR_e-, S or O;

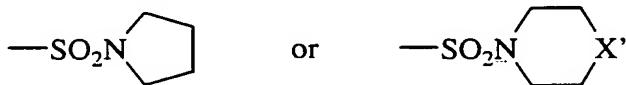
R is hydrogen, halogen, -OH, alkoxy, or -NR_kR_l, where R_k and R_l are independently selected from hydrogen and alkyl.

In the compounds of formula (IIIB), R₁ and R₂ are together alkylene of about 4 to about 8 carbons, optionally substituted with a group R', where R' is selected from -OH, halogen, -NR_aR_b, in which R_a and R_b are independently selected from hydrogen, -C(=O)R_c, -SO₂R_d and -C(=O)(CH₂)_mCO₂R_e, in which R_c and R_d are independently selected from alkyl, aryl and heteroaryl, R_e is hydrogen or alkyl and m is an integer from 1 to 3. Preferably, substituent group R' is in the S configuration, and m is 1. Also in preferred embodiments, R₁ and R₂ are together unsubstituted alkylene of about 4 to about 6 carbons or alkylene of about 4 to about 6 carbons substituted with -OH or alkoxy. In more preferred embodiments, R₁ and R₂ are together -(CH₂)₄- or -CH₂CH(OH)(CH₂)₂-.

In the compounds of formula (IIIB), Ar is mono-, di-, tri-, or tetra-substituted phenyl, wherein said substituents are independently selected from halogen; alkyl; alkoxy; aryloxy; aralkyloxy; alkylene dioxide; -OH; -SO₂R_f in which R_f is alkyl or aryl; -CN; haloalkyl; -NR_gR_h, in which R_g and R_h are independently selected from hydrogen, alkyl, -C(=O)R_f, -C(=O)-N(R_e)₂, -S(O)₂R_f, and -(CH₂)_y-CO₂R_e in which y is an integer from 1 to 3; -S(O)₂N(R_i)(R_j), in which R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with -CO₂R_e, aryl and aralkyl; or R_i and R_j together form -(CH₂)₂X(CH₂)₂-, where X is a direct bond, -CH₂-, -NR_e-, S or O. In preferred embodiments, Ar is mono-, di-, tri-, or tetra-substituted phenyl,

wherein said substituents are independently selected from alkyl; alkoxy; aralkyloxy; alkylene dioxide; -OH; haloalkyl; -NR_gR_h, in which R_g and R_h are independently selected from hydrogen, alkyl, and -S(O)₂R_f; -S(O)₂N(R_i)(R_j), where R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with -CO₂R_e, and aralkyl; or R_i and R_j together form

5 -(CH₂)₂X(CH₂)₂-, where X is a direct bond, -NR_e-, S or O. In more preferred embodiments, Ar is mono-, di-, tri-, or tetra-substituted phenyl, wherein said substituents are independently selected from lower alkyl; -OCH₃; -OCH₂C₆H₅; -OCH₂O; -OH; -CF₃; -N(SO₂CH₃)₂; -NHSO₂CH₃; -SO₂N(CH₃)₂; -SO₂N(CH₃)(CH₂CO₂H); -SO₂NHCH₃; -SO₂N(CH₃)(CH₂C₆H₅);



10

where X' is -N(CH₃)- or -O-.

In the compounds of formula (IIIB), n is an integer from 1 to 3. Preferably, n is 1.

In certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB), except that when n is 1, R₁ and R₂ are unsubstituted alkylene of 4 carbons (*i.e.*, -(CH₂)₄), and R is H, then Ar is other than 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-amino-4,5-dichlorophenyl, 3,4-dichlorophenyl, 2-amino-4-trifluoromethyl, 2-N(SO₂CH₃)₂-phenyl, 3-N(SO₂CH₃)₂-phenyl, 4-N(SO₂CH₃)₂-phenyl, 2-NHSO₂CH₃-phenyl, 3-NHSO₂CH₃-phenyl, 4-NHSO₂CH₃-phenyl, 2-N(SO₂CH₃)₂-4,5-dichlorophenyl, 2-N(SO₂CH₃)₂-4-trifluoromethylphenyl, 2-NHSO₂CH₃-4-trifluoromethylphenyl, 4-SO₂CH₃-phenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3,4,5-trimethoxyphenyl, 2-NHSO₂CH₃-4,5-dichlorophenyl, 2-NHCO₂H-4-trifluoromethylphenyl, 2-NH(SO₂C₆H₅)-phenyl, 3-SO₂NHCH₃-4-chlorophenyl, 3-SO₂NH₂-4-chlorophenyl, 3-SO₂NHCH₃-4-fluorophenyl, 4-SO₂NHCH₃-phenyl, 3-SO₂NHCH₃-phenyl, 2-SO₂NHCH₃-phenyl, 2-SO₂NHCH₃-4-bromophenyl, 2-methoxy-3-SO₂NHCH₃-phenyl, 4-methoxy-3-SO₂NHCH₃-phenol, 2-N(CH₂CO₂H)₂-4-trifluoromethylphenyl, 3,4-dihydroxyphenyl, 3,4-dimethoxyphenyl, 2-SO₂N(CH₃)CH₂C₆H₅-4,5-dimethoxyphenyl, 2-fluorophenyl, or 4-fluorophenyl, 2-SO₂NCH₃-CH₂CO₂H-3,4-olimethoxyphenol.

Also in certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB), except that when n is 1, R¹ and R₂ are unsubstituted alkylene of 4

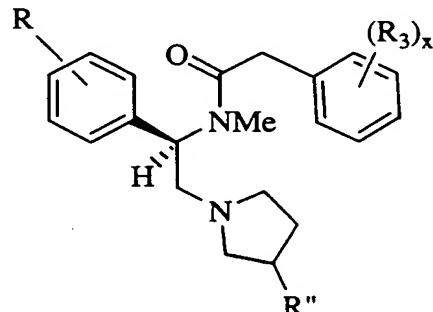
carbons, and R is NH₂, then Ar is other than 3,4-dichlorophenyl, 2-aminophenyl or 4-N(SO₂CH₃)₂-phenyl.

In still other preferred embodiments, compounds of the present invention have the structure of formula (IIIB), except that when n is 1, R₁ and R₂ are -CH₂CH(OH)(CH₂)₂- , and R is hydrogen, then Ar is other than 2-amino-4-trifluoromethylphenyl, aminophenyl, 4-SO₂CH₃-phenyl, 3,4,5-trimethoxyphenyl, 2-SO₂NHCH₃-phenyl, trifluoromethylphenyl, methylphenyl, halophenyl, methoxyphenyl, unsubstituted phenyl, 3-chloro-4-hydroxyphenyl, 4-benzyloxyphenyl, hydroxyphenyl, aminochlorophenyl, aminobromophenyl, acetamidophenyl, methylsulfonylaminophenyl, formamidophenyl or 3-amino-4-methoxyphenyl.

10 Also in other preferred embodiments, compounds of the invention have the structure of formula (IIIB), except that when n is 1, R₁ and R₂ are -CH₂CH(OH)(CH₂)₂- , and R is hydroxy or amino, then Ar is other than trifluoromethylphenyl.

15 In yet other preferred embodiments, compounds of the present invention have the structure of formula (IIIB), except that when n is 1, R₁ and R₂ are unsubstituted alkylene of 4 carbons, and R is OH or OCH₃, then Ar is other than 2-NHSO₂CH₃-phenyl, 4-trifluoromethylphenyl, or 3,4-dichlorophenyl.

In preferred form, the compounds of formula (IIIB) have the following formula (IIIB-i).



20

(IIIB-i)

wherein:

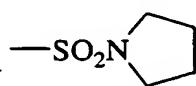
x is an integer from 0 to 4;

25 R'' is hydrogen, fluoro, -OH, -NHC(=O)R_c, -NHSO₂R_d and -NHC(=O)(CH₂)_mCO₂R_e, in which R_c and R_d are independently selected from alkyl, aryl and heteroaryl, R_e is hydrogen or alkyl and m is an integer from 1 to 3

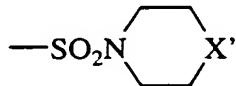
5 R_3 is independently selected from halogen; alkyl; alkoxy; aryloxy; aralkyloxy; alkylene dioxide; -OH; $-SO_2R_f$ in which R_f is alkyl or aryl; -CN; haloalkyl; $-NR_gR_h$, in which R_g and R_h are independently selected from hydrogen, alkyl, $-C(=O)R_f$, $-C(=O)-N(R_e)_2$, $-S(O)_2R_f$ in which R_f is alkyl or aryl, and $-(CH_2)_y-CO_2R_e$ in which y is an integer from 1 to 3; $-S(O)_2N(R_i)(R_j)$, in which R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with $-CO_2R_e$, aryl and aralkyl; or R_i and R_j together form $-(CH_2)_2X(CH_2)_2-$, where X is a direct bond, $-CH_2-$, $-NR_e-$, S or O;

10 R is hydrogen, halogen, -OH, alkoxy, or $-NR_kR_l$, where R_k and R_l are independently selected from hydrogen and alkyl.

15 In the above formula (IIIB-i), R_3 is independently selected from halogen; alkyl; alkoxy; aryloxy; aralkyloxy; alkylene dioxide; -OH; $-SO_2R_f$ in which R_f is alkyl or aryl; -CN; haloalkyl; $-NR_gR_h$, in which R_g and R_h are independently selected from hydrogen, alkyl, $-C(=O)R_f$, $-C(=O)-N(R_e)_2$, $-S(O)_2R_f$ in which R_f is alkyl or aryl, and $-(CH_2)_y-CO_2R_e$ in which y is an integer from 1 to 3; $-S(O)_2N(R_i)(R_j)$, in which R_i and R_j are each independently selected from hydrogen, alkyl optionally substituted with $-CO_2R_e$, aryl and aralkyl; or R_i and R_j together form $-(CH_2)_2X(CH_2)_2-$, where X is a direct bond, $-CH_2-$, $-NR_e-$, S or O. In preferred embodiments, R_3 is independently selected from alkyl; alkoxy; aralkyloxy; alkylene dioxide; -OH; haloalkyl; $-NR_gR_h$, in which R_g and R_h are independently selected from hydrogen, alkyl, and $-S(O)_2R_f$; $-S(O)_2N(R_i)(R_j)$, in which R_i and R_j are each independently selected from hydrogen, alkyl 20 optionally substituted with $-CO_2R_e$, and aralkyl; or R_i and R_j together form $-(CH_2)_2X(CH_2)_2-$, where X is a direct bond, $-NR_e-$, S or O. In more preferred embodiments, R_3 is independently selected from lower alkyl; $-OCH_3$; $-OCH_2C_6H_5$; $-OCH_2O-$; -OH; CF_3 ; $-N(SO_2CH_3)_2$; $-NHSO_2CH_3$; $-SO_2N(CH_3)_2$; $-SO_2N(CH_3)(CH_2CO_2H)$; $-SO_2NHCH_3$; $-SO_2N(CH_3)(CH_2C_6H_5)$;



or



where X' is $-N(CH_3)-$ or $-O-$.

Also in the above formula (IIIB-i), R is hydrogen, halogen, -OH, alkoxy, or $-NR_kR_l$, where R_k and R_l are independently selected from hydrogen and alkyl. In preferred embodiments, R is hydrogen, halogen, -OH or alkoxy.

In the compounds of formula (IIIB-i), n is an integer from 1 to 3. Preferably, n is 1.

30 Also in the above formula (IIIB-i), R' is preferably in the S configuration, and m is preferably 1.

In certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB-i), except that when R and R" are H, then the phenyl ring and (R₃)_x together are other than 2-aminophenyl, 3-aminophenyl, 4-aminophenyl, 2-N(SO₂CH₃)₂-phenyl, 3-N(SO₂CH₃)₂-phenyl 4-N(SO₂CH₃)₂-phenyl, 2-NHSO₂CH₃-phenyl, 3-NHSO₂CH₃-phenyl, 4-NHSO₂CH₃-phenyl, 4-SO₂CH₃-phenyl, 2-methoxyphenyl, 2-hydroxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl, 3-SO₂NHCH₃-phenyl, 2-SO₂NHCH₃-phenyl, 4-SO₂NHCH₃-phenyl, 2-fluorophenyl, 4-fluorophenyl, 3,4-dichlorophenyl, 2-amino-4-trifluoromethyl, 2-N(SO₂CH₃)₂-4-trifluoromethylphenyl, 2-NHSO₂CH₃-4-trifluoromethylphenyl, 2-NHCH₂CO₂H-4-trifluoromethylphenyl, 3-SO₂NHCH₃-4-chlorophenyl, 10 3-SO₂NH₂-4-chlorophenyl, 3-SO₂NHCH₃-4-fluorophenyl, 2-SO₂NHCH₃-4-bromophenyl, 2-methoxy-3-SO₂NHCH₃-phenyl, 4-methoxy-3-SO₂NHCH₃-phenol, 2-N(CH₂CO₂H)₂-4-trifluoromethylphenyl, 3,4-dihydroxyphenyl, 3,4-dimethoxyphenyl, 2-amino-4,5-dichlorophenyl, 2-N(SO₂CH₃)₂-4,5-dichlorophenyl, 3,4,5-trimethoxyphenyl, 2-NHSO₂CH₃-4,5-dichlorophenyl, or 2-SO₂N(CH₃)CH₂C₆H₅-4,5-dimethoxyphenyl, 2-SO₂(CH₃)-CH₂CO₂H-3,4-dimethoxyphenol.,

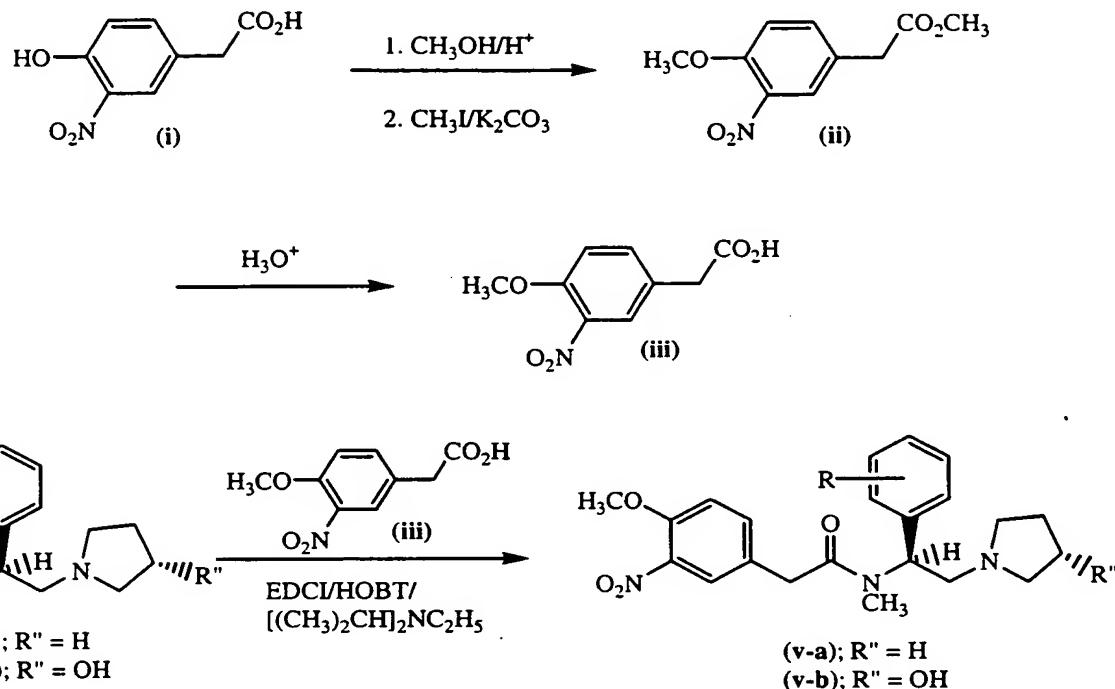
15 In other certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB-i), except that when R" is H and R is NH₂, then the phenyl ring and (R₃)_x together are other than 3,4-dichlorophenyl, 2-aminophenyl or 4-N(SO₂CH₃)₂-phenyl.

In still other certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB-i), except that when R" is OH and R is hydrogen, then the phenyl ring and (R₃)_x together are other than unsubstituted phenyl, 2-amino-4-trifluoromethylphenyl, aminophenyl, 4-SO₂CH₃-phenyl, 3,4,5-trimethoxyphenyl, 2-SO₂NHCH₃-phenyl, trifluoromethylphenyl, methylphenyl, halophenyl, methoxyphenyl, 3-chloro-4-hydroxyphenyl, 4-benzyloxyphenyl, hydroxyphenyl, aminochlorophenyl, aminobromophenyl, acetamidophenyl, methylsulfonylaminophenyl, formamidophenyl or 3-amino-4-methoxyphenyl.

25 Also in other certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB-i), except that when R" is OH and R is hydroxy or amino, then the phenyl ring and (R₃)_x together are other than trifluoromethylphenyl.

In yet other certain preferred embodiments, compounds of the present invention have the structure of formula (IIIB-i), except that when R" is H and R is OH or OCH₃, then the phenyl ring and (R₃)_x together are other than 2-NHSO₂CH₃-phenyl, 4-trifluoromethylphenyl or 3,4-dichlorophenyl.

Preparatory for the compounds of formula IIIB and IIIB-i, the following intermediates were prepared.



5

4-Methoxy-5-nitrophenyl acetic acid (iii):

10 To a solution of 4-hydroxy-5-nitrophenyl acetic acid (20.0 g, 0.101 mol) in anhydrous methanol (500 mL) was added Dowex 50Wx4-400 (H^+) resin, pre-washed with methanol. The suspension was stirred with refluxing for 24 hr. The resin was filtered and the filtrate was evaporated to dryness to give as a light yellow oil; 21.3 g (99.3%). The ester was used directly in the following reaction.

15 The above ester (21.3 g, 0.1 mol) was redissolved in anhydrous acetone (250 mL) and anhydrous potassium carbonate (20.94 g, 0.14 mol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for 15 minutes followed by slow addition of methyl iodide (20.1 g, 0.14 mol) and the stirring was continued for an additional 48 h at room temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness. The residue was portioned between CH_2Cl_2 and water. The organic layer was separated and washed with water and saturated salt solution, and was dried over anhydrous sodium sulfate. Evaporation to dryness afforded (ii) as a yellow solid; 23.0 g (100%); ¹H NMR (CDCl_3 , 300 MHz) δ 3.62 (s,

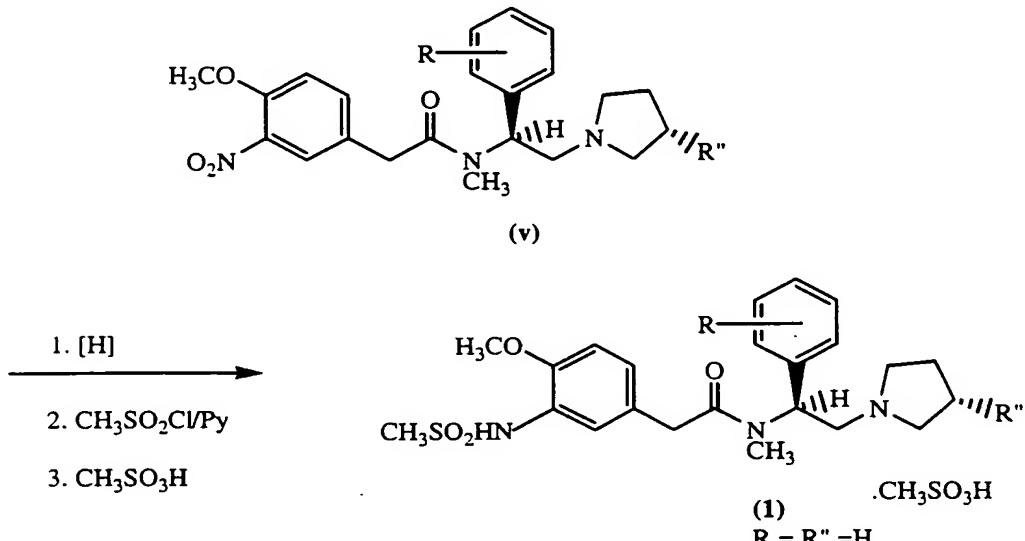
2H), 3.72 (s, 3H), 3.96 (s, 3H), 7.05 (d, J = 8.5 Hz, 1H), 7.48 (m, 1H), 7.80 (d, J = 2.2 Hz, 1H).

The compound was used in next step without any further purification.

A suspension of ester (ii) (23.0 g) in 4N HCl (300 mL) and acetic acid (20 mL) was heated to reflux with stirring for 18 h. The reaction mixture was cooled to room temperature and the resulting solid was filtered, washed with water, and dried to give the acid (iii) as a light yellow solid, 17.5 g (81%); ^1H NMR (d_6 DMSO, 300 MHz) δ 3.63 (s, 2H), 3.89 (s, 3H), 7.28 (d, J = 8.5 Hz, 1H), 7.50 (m, 1H), 7.77 (d, J = 2.0 Hz, 1). Acid (iii) was sufficiently pure to use in the coupling reaction, discussed *infra*.

10 2-(4-Methoxy-5-nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]-acetamide (va)

To a solution of acid (iii) (17.5 g, 85.78 mmol) in anhydrous CH_2Cl_2 (175 mL) was added 1-hydroxybenzotriazole hydrate (11.58 g, 85.78 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI, 18.02 g, 94.36 mmol). After stirring the reaction mixture at room temperature for 30 min, a solution of the diamine (iv-a) (16.00 g, 78.43 mmol) in anhydrous CH_2Cl_2 (60 mL) was added, followed by N,N-diisopropylethylamine (10.43 g, 80.0 mmol). The reaction mixture was stirred at room temperature for 72 h. The reaction mixture was quenched with saturated sodium bicarbonate solution and the organic layer was separated, washed with saturated salt solution and dried over anhydrous sodium sulfate. The removal of CH_2Cl_2 under reduced pressure gave crude compound (v-a) as dark brown oil. The product (v-a) was purified on a silica gel column to give a yellow syrup, 31 g (99%); ^1H NMR(CDCl_3 , 300 MHz) δ 1.74 (m, 4H), 2.75 (s, 3H), 3.95 (s, 3H), 6.10 (m, 1H), 7.05-7.75 (m, 8H).

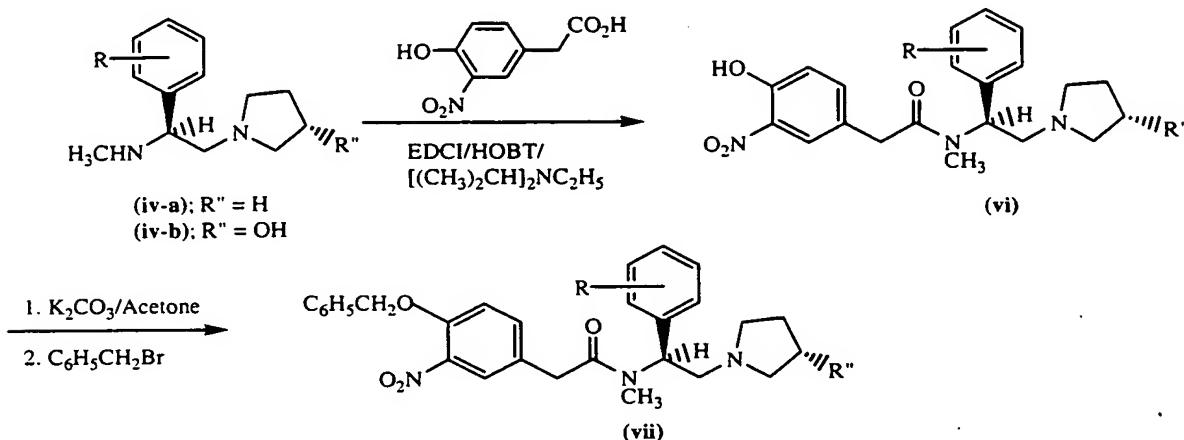
Example 1222-(3-N-Methylsulfonamido-3-amino-4-methoxyphenyl)-N-methyl-N-[*(1S*)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide methane sulfonate (1)

5

To a solution of compound (v) (31.0 g, 78.0 mmol) in ethanol (700 mL) at 50-60°C was added hydrazine hydrate (15 mL) followed by Raney/Nickel slowly until all the starting material was reduced, as shown by TLC. The reaction mixture was cooled to room temperature and the catalyst was filtered off and washed thoroughly with warm ethanol. The filtrate was evaporated to dryness to give the amino compound, which was used directly in the following reaction.

To a stirred solution of the amino compound (26.6 g, 72.45 mmol) in anhydrous CH_2Cl_2 (250 mL) was added pyridine (12.1 g, 152.6 mmol) and the reaction mixture was cooled to 0-5°C in an ice-bath. A solution of methanesulfonyl chloride (13.1 g, 114.4 mmol) in anhydrous CH_2Cl_2 (50 mL) was added dropwise in 15 min with continued stirring. After the completion of the addition, the ice-bath was removed and the reaction mixture was stirred at room temperature for 60 h. The reaction was quenched by the slow addition of saturated sodium bicarbonate, and the organic layer was separated, washed with water, saturated salt solution and dried over anhydrous sodium sulfate. The removal of solvent gave the crude free base of compound (1), which was purified on a silica gel column. The methane sulfonic acid salt was prepared and recrystallized twice from 2-propanol to give (1) as an off-white solid, 19.7 g (50%); mp 149-151°C; ^1H NMR (d_6DMSO , 300 MHz) δ 2.01 (m, 4H), 2.38 (s, 3H), 2.73 (s, 3H), 2.93 (s, 3H), 3.17 (m, 2H), 3.81 (s, 3H), 6.15 (m, 1H), 7.00-7.34 (m, 8H), 8.90 (s, 1H); MS 446 ($\text{M}+\text{H}$)⁺.

Intermediates for the compounds prepared in following examples were prepared as depicted below.



5

2-(4-Hydroxy-5-nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (vi)

The diamine (iv-a) was condensed with 4-hydroxy-5-nitrophenyl acetic acid following the method described for compound (v). The product (vi) was isolated as a hydrochloride salt in 10 60% yield; ¹H NMR (CDCl₃, 300 MHz) δ 2.00-2.40 (m, 4H), 2.93 (s, 3H), 3.65 (d, J = 9.0 Hz, 1H), 4.05 (m, 4H), 4.38 (d, J = 9.5 Hz, 1H), 6.40 (m, 1H), 7.05-7.50 (m, 6, H), 7.70 (d, J = 5.5 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H). Intermediate compound (vi) was then used in the preparation of intermediate (vii).

15

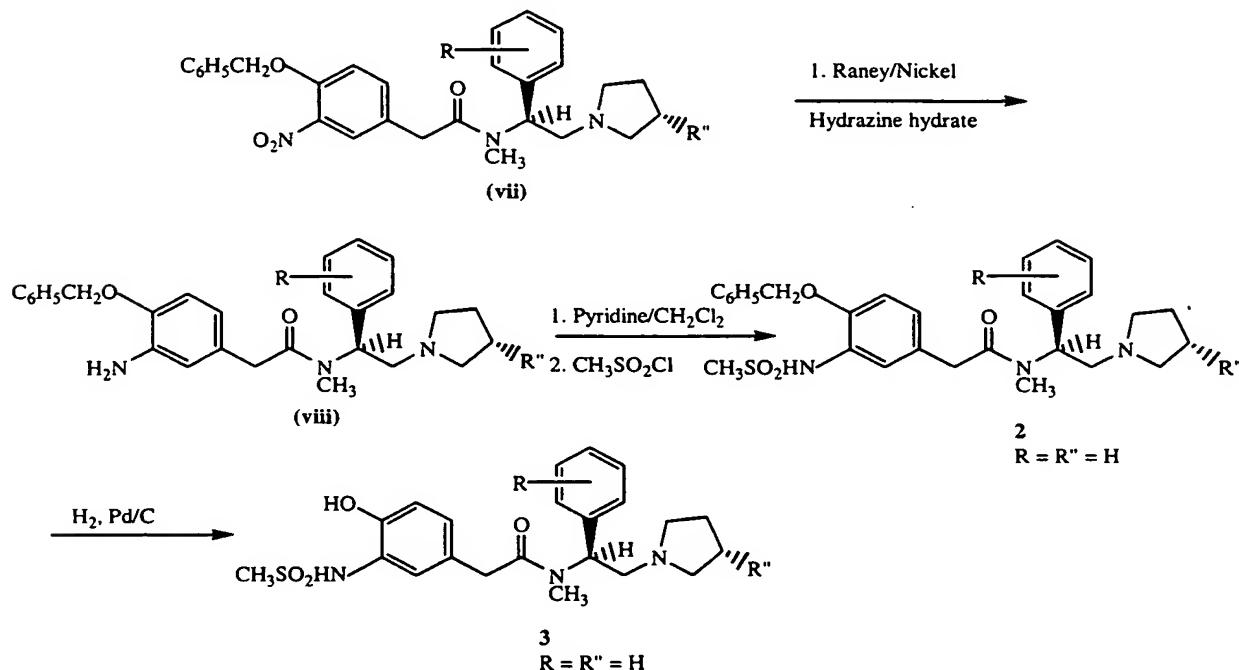
2-(4-Benzyl-5-nitrophenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (vii)

To a solution of compound (vi) (3.2 g, 7.62 mmol) in anhydrous acetone (50 mL) was added anhydrous potassium carbonate (4.22 g, 30.5 mmol). The mixture was stirred at room 20 temperature for 30 mins then added dropwise benzyl bromide (1.30 g, 7.62 mmol). The stirring was continued for an additional 48 h and the reaction mixture was filtered off. The cake was washed thoroughly with acetone and the combined filtrate was evaporated to dryness. The residue was redissolved in CH₂Cl₂ and the organic layer was washed with water, saturated salt solution and dried over anhydrous sodium sulfate. The removal of the solvent resulted in a

yellow foam, and the product was purified on a silica gel column to give (vii) as a solid, 2.5 g (69%); MS 474 ($M+H$)⁺.

Intermediate compound (vii) was then used to prepare compounds 2 and 3 of the present invention, as depicted below.

5



Example 123

10 **2-(3-N-Methylsulfonamido-3-amino-4-benzyloxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (2)**

Compound (viii) and compound (2) were prepared according to the procedure described for (v). Compound (2) was isolated as a hydrochloride salt in 95% yield (HCl salt); mp 219-221°C; MS 522 ($M+H$)⁺; ¹H NMR (d₆DMSO, 300 MHz) δ 2.00 (m, 4H), 2.78 (s, 3H), 2.90 (s, 3H), 3.15 (m, 2H), 3.70 (m, 5H), 4.05 (m, 1H), 5.16 (s, 2H), 6.15 (m, 1H), 7.07-7.53 (m, 14H), 8.94 (s, 1H).

Example 124**2-(3-N-Methylsulfonamido-3-amino-4-hydroxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide (3)**

5 To a solution of compound (2) (2.4 g, 4.6 mmol) in ethanol (150 mL) was added 10%Pd/C (0.25 g), and the resulting suspension was hydrogenated at room temperature for 24 h. The catalyst was removed by filtration and washed with hot methanol. The combined filtrate was evaporated to dryness to give a solid, which was recrystallized from acetonitrile to give compound (3) as a white solid, 1.6 g (72%) (HCl salt); mp 228-230°C; MS 432 (M+H)⁺; ¹H NMR (d₆DMSO, 300 MHz) δ 1.98 (m, 4H): 2.76 (s, 3H), 2.93 (s, 3H) 3.17 (m, 2H), 3.44-4.00 (m, 6H), 6.14 (m, 1H), 6.80-7.37 (m, 7 H), 8.70 (s, 8H).

10

Employing similar chemistry, the following compounds of formula IIIB were prepared.

Example 125**2-(2-N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]]acetamide**

15 Prepared from diamine (iv-b) in 31% yield (HCl salt); mp 168-171°C; MS (FAB) 432 (MH)⁺.

20

Example 126**2-(2-N-Methylsulfonamido-2-amino-4-trifluoromethylphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]]acetamide**

25 Prepared from diamine (iv-b) in 18% yield (HCl salt); mp 178-181°C; MS (FAB) 500 (MH)⁺.

30

Example 127**2-(3-N-Methylsulfonamido-3-amino-4-methoxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]]acetamide**

35 Prepared from diamine (iv-b) in 44% yield (HCl salt); mp 148-151°C; MS (FAB) 462 (MH)⁺.

Example 1282-(2-N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-1-(4-methoxyphenyl)-2-(1-pyrrolidinyl)ethyl]acetamide

5 Prepared from the diamine (iv-a) (R = 4-OCH₃) in 40% yield (CH₃SO₃H salt); mp 170-172°C; MS 446 (M+H)⁺; ¹H NMR (d₆DMSO, 300 MHz) δ 1.90 (m, 4H), 2.34 (s, 3H), 2.70 (s, 3H), 2.98 (s, 3H), 3.20 (m, 2H), 3.60 (m, 4H), 3.75 (s, 3H), 4.07 (m, 2H), 6.10 (m, 1H), 6.93 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.29 (m, 4H), 9.06 (s, 1H).

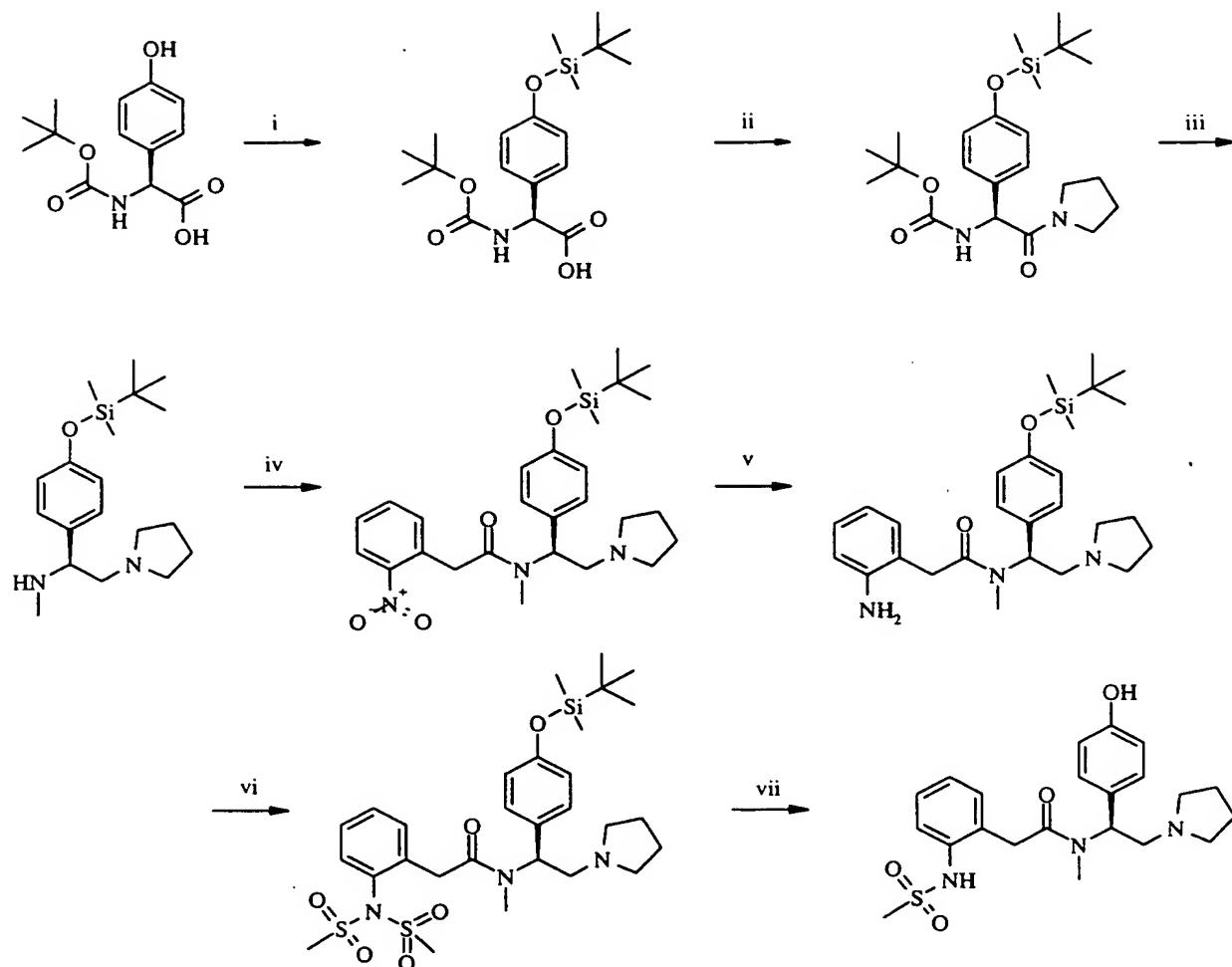
10

Example 129A(R,S)-2-(2-N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-1-(4-hydroxyphenyl)-2-(1-pyrrolidinyl)ethyl]acetamide

15 To a solution of the compound prepared in Example 128 (1.07 g, 2.04 mmol) in CH₂Cl₂ (20 mL) at -70°C under a nitrogen atmosphere was added dropwise a solution of BBr₃ 1M in CH₂Cl₂ (7.95 mL, 7.93 mmol). The reaction mixture was stirred for 1 additional hour and was slowly warmed to room temperature. After stirring for 24h, the reaction mixture was then quenched with anhydrous methanol (10 mL). The solvent was removed under reduced pressure, 20 and the resulting residue was stirred in methanol:ether (1:1) to give a solid. The solid was re-dissolved in CH₂Cl₂ and basified to give the free base of the title compound. The methane sulfonic acid salt was prepared to give the title compound in 83% yield (CH₃SO₃H salt); mp 197-199°C; ¹H NMR (d₆DMSO, 300 MHz, HBr Salt) δ 1.93 (m, 4H), 2.70 (m, 3H), 2.98 (m, 3H), 3.16 (m, 2H), 3.60 (m, 4H), 3.73 (d, J = 14.0 Hz, 1H), 4.05 (d, J = 14.5 Hz, 1H), 6.02 (m, 2H), 6.74 (d, 25 8.0 Hz, 2H), 7.04 (d, J = 8.3 Hz, 2H), 7.27 (m, 4H), 9.07 (s, 1H).

The preparation of the compound of Example 129B follows according to the following Scheme P.

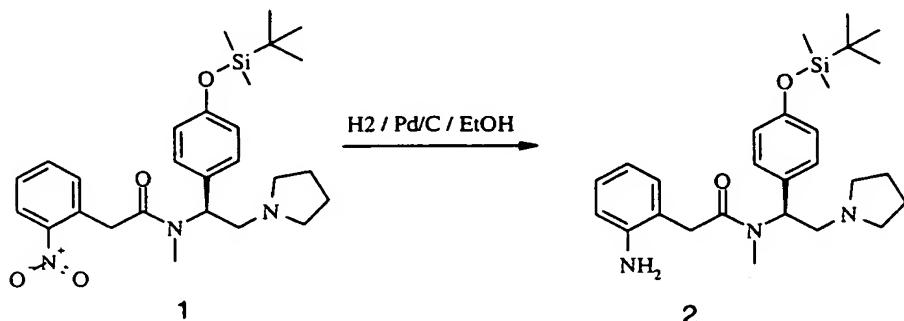
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Scheme P

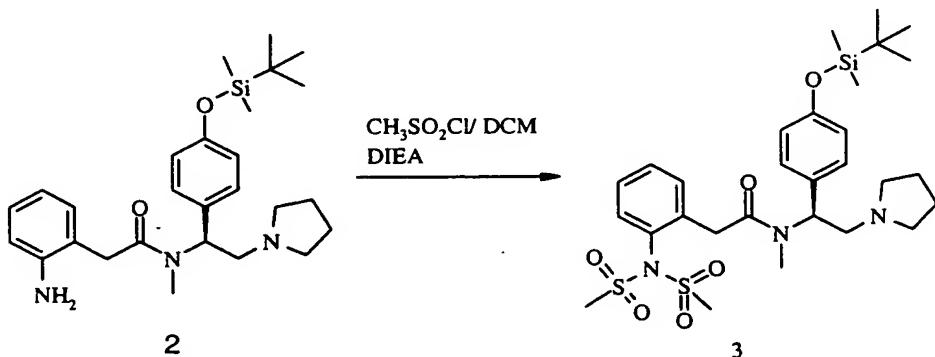
Key: i. (tert)-Butyldimethylsilyl chloride, imidazole, DMF, 0 °C→25 °C, 2h. ii. DCC, HOBr, pyrrolidine, DCM, rt, 3 h. iii. LAH, THF, 0 °C→35 °C, 8h. iv. DCC, HOBr, 2-nitrophenylacetic acid, DMF, rt, 3h. v. 10% Pd on C, EtOH, H₂ gas, rt, 12h. vi. CH₃SO₂Cl, DCM, DIEA, 0 °C→25 °C, 2h. vii. TBAF, THF, rt, 2h.

Example 129B
(S)-2-(2-N-Methylsulfonamido-2-aminophenyl)-N-methyl-N-1-(4-hydroxyphenyl)-2-(1-pyrrolidinyl)ethyl]acetamide

5



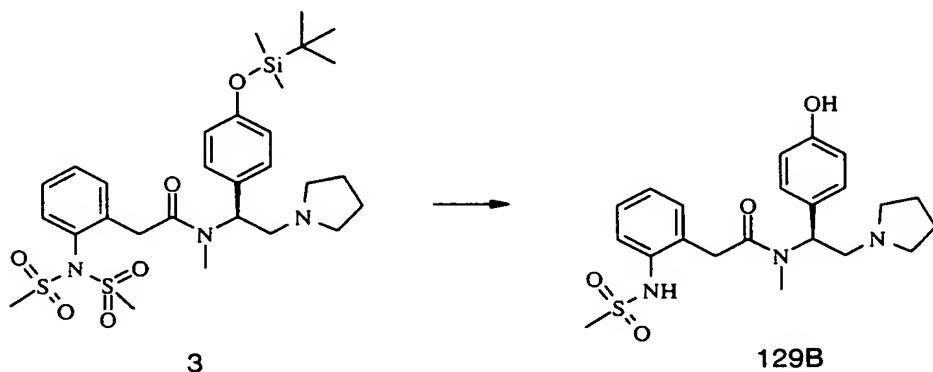
Starting nitro phenyl derivative 1 (2.28 g; 4.58 mmol) was dissolved in ethanol (100 mL). The reaction vessel was evacuated under reduced pressure and purged with nitrogen. 10% Pd on C was added to the reaction mixture. The mixture was evacuated under reduced pressure and put over hydrogen via a balloon. The reaction proceeded to completion after 4-6 h, following the disappearance of the starting material by TLC (R_f SM = 0.5; R_f Prod = 0.48; 2% MeOH in DCM). The reaction mixture was filtered through Celite, and concentrated to give the product amine. Purification of the product amine 2 by column chromatography afforded 1.14g (2.4 mmol; 53%) yield.



Starting amine 2 (1.0 g; 2.16 mmol) was dissolved in DCM. DIEA (1.16 mL; 6.49 mmol) was added to the reaction vessel and the mixture was cooled to 0 °C with an ice bath. Mesyl chloride (0.37 mL; 4.76 mmol) was added drop-wise to the mixture at 0 °C, after which the reaction mixture was allowed to warm to ambient temperature. The reaction proceeded for 1

hour after which the starting material disappeared by TLC (R_f SM = 0.6; R_f prod = 0.8; 10% MeOH in DCM). The reaction was diluted with ethylacetate, washed with water, brine, then dried over $MgSO_4$. The mixture was filtered and concentrated to yield product **3** (1.3 g; 2.08 mmol; 96%), which was used crude in the next step.

5



Amine 3 from the above reaction (1.3 g; 2.08 mmol) was dissolved in THF (20 mL). A THF solution of TBAF (1M solution in THF ; 4.16mL; 4.16 mmol) was added to the reaction mixture, and the mixture was stirred at room temperature for 2h monitoring the disappearance of the starting material (R_f SM = 0.8; R_f prod = 0.4; 10% MeOH in DCM). Phenol 129B was obtained after standard work-up and purification by silica gel chromatography. LCMS: M+H = 432. Elemental analysis (CHN): C₂₂H₂₉N₃O₄S.H₂O (calc %C = 58.78; %H = 6.95; %N = 9.35; %S = 7.13; found %C = 58.55; %H = 6.83; %N = 8.94; %S = 7.27).

15

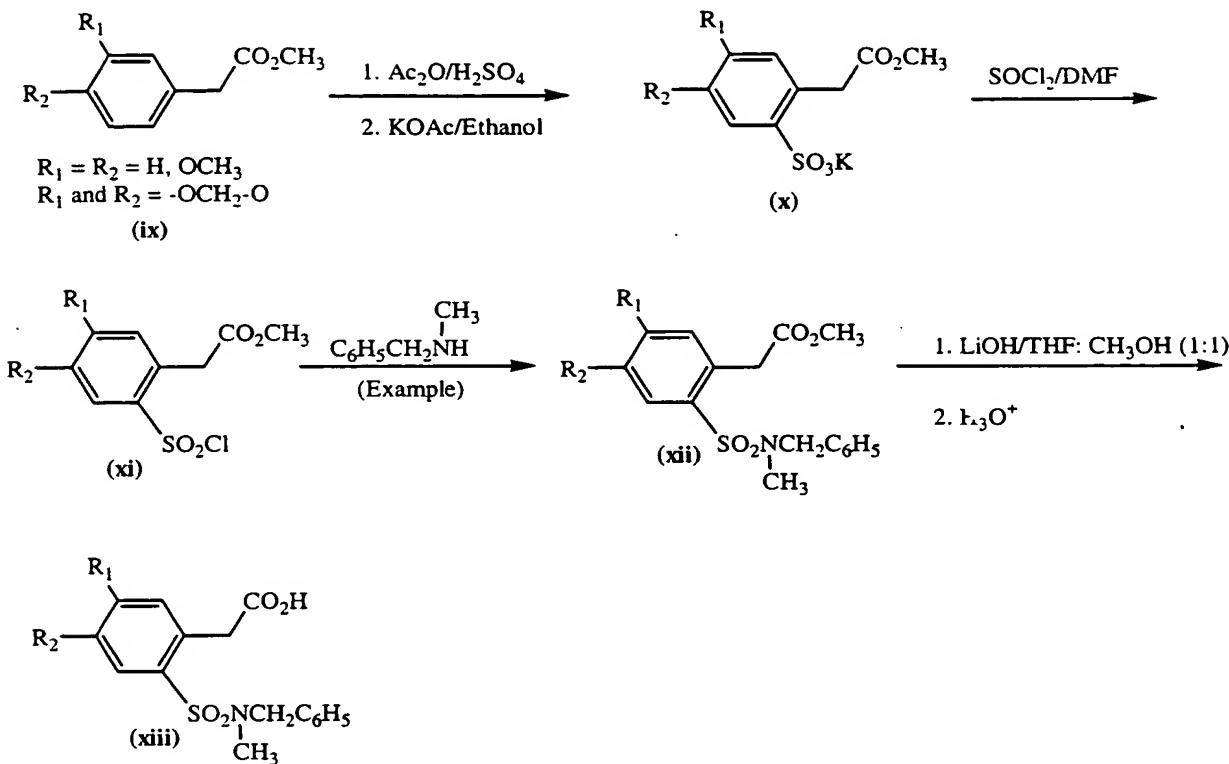
Example 130

2-(3-N-Bis-methylsulfonamido-3-amino-4-hydroxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide

20 The title compound was prepared from 2-(2-amino-4-hydroxyphenyl)-N-methyl-N-[(1S)-1-phenyl-2-(1-pyrrolidinyl)ethyl]acetamide and methane sulfonyl chloride as described above in 83% yield. The title compound was isolated as the methane sulfonic acid salt; mp 197-199°C (CH₃SO₃H salt); MS (FAB) 510 (M+H)⁺; ¹H NMR (d₆DMSO, 300 MHz) δ 2.05 (m, 4H), 2.36 (s, 3H), 2.75 (s, 3H), 3.05 (s, 3H), 3.51 (s, 3H), 6.15 (m, 1H), 7.35 (m, 5H), 9.5 (bs, 1H).

25 The following general chemistry was employed in the preparation of sulfonyl chloride derivatives, as described in *J. Heterocyclic Chem.*, **29**, 1667-1669 (1992), similar to methods

described hereinabove, in the preparation of compounds of formula IIIB and IIIB-i, as prepared in Examples 131 to 147.



5

To a solution of the ester derivatives (ix) (10.3 mmol) and acetic anhydride (30.7 mmol) in ethyl acetate (15.3 mL) was added, dropwise, a solution of concentrated sulfuric acid (11.2 mmol) in ethyl acetate (4.1 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 h, after which a solution of potassium acetate (11.2 mmol) in 95% ethanol was added and the mixture was stirred for additional 30 min at room temperature. The potassium salt (x) (90%) was isolated by filtration and used in the next reaction.

A solution of thionyl chloride (8.74 mmol) and anhydrous DMF (0.01 mL) was added to potassium salt (x) (1.6 mmol) under a nitrogen atmosphere. The reaction mixture was stirred at 60°C for 3.5 h and then poured into an ice water mixture and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extract was dried and evaporated to dryness to give (xi) (81%). The material was used in the following reaction.

To a solution of 70 mmol of an appropriate amine (N-benzylmethylamine in the presently exemplified chemistry) in anhydrous THF (30 mL) at 0°C under a nitrogen atmosphere was added

dropwise a solution of (xi) (31.7 mmol) in anhydrous THF (30 mL). After the addition was complete, the reaction mixture was stirred at room temperature for 20h. The resulting solid was filtered off, the cake was washed with THF and the filtrate was evaporated to dryness. The residue was portioned between CH_2Cl_2 and water. The organic layer was separated, dried over anhydrous sodium sulfate and evaporated to dryness to give (xii) in 88% yield. The compound was used directly into the hydrolysis reaction.

5 To a solution of (xii) (3 mmol) in tetrahydrofuran:methanol (1:1, 5 mL) at 0-5°C was added 1M lithium hydroxide (6 mL) and the reaction mixture was stirred at this temperature for 1 h then at room temperature for 24 h. After neutralization of the solution with concentrated HCl, 10 the solvent was removed under reduced pressure to give a white solid. The solid was filtered off, washed with water and dried to give (xiii), (95%); ^1H NMR ($\text{R}_1 = \text{R}_2 = \text{OCH}_3$; CDCl_3 , 300 MHz) δ 2.61 (s, 3H), 3.87 (s, 3H), 3.90 (s, 3H), 4.08 (s, 2H), 4.27 (s, 2H), 6.85 (s, 1H), 7.31 (m, 5H), 7.49 (s, 1H).

15 The compounds of Examples 131 to 147 were prepared employing the general procedure described for compound (v). Crude compounds were purified on a silica gel column and isolated as salts either from hydrochloric acid or methane sulfonic acid.

Example 131

20 2-[2-(N-Benzyl-N-methylsulfamoyl)-4,5-methylenedioxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[(1-pyrrolidinyl)ethyl]]acetamide

Yield, 82% ($\text{CH}_3\text{SO}_3\text{H}$ salt); mp 236-238°C; ^1H NMR (d_6DMSO , 300 MHz) δ 1.98 (m, 4H), 2.48 (s, 3H), 2.55 (s, 3H), 2.74 (s, 3H), 3.10-3.75 (m, 6H), 4.05-4.40 (m, 4H), 6.10 (m, 1H), 6.16 (bs, 2H), 7.05 (s, 1H), 7.35 (m, 11H), 9.30 (bs, 1H).

25

Example 1322-[2-(N-Dimethylsulfamoyl)-4,5-methylenedioxypyhenyl]-N-methyl-N-[(1S)-1-phenyl-2-[(1-pyrrolidinyl)ethyl]]acetamide

5 Yield, 48% (HCl salt); mp 269-271°C; ^1H NMR (CDCl_3 , 300 MHz) δ 1.96 (m, 4H), 2.25 (m, 2H), 2.69 (s, 6H), 2.92 (bs, 3H), 4.05 (m, 4H), 4.35 (q, J = 10.0 Hz, 2H), 6.03 (d, J = 9.5 Hz, 2H), 6.35 (m, 1H), 7.27 (m, 7H).

Example 1332-[2-(N-Dimethylsulfamoyl)-4,5-methylenedioxypyhenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrrolidinyl)ethyl]]acetamide

10 Prepared from diamine (iv-b), yield, 41% (HCl salt); mp >240°C (d); MS 491 ($\text{M}+\text{H}$) $^+$.

Example 1342-[2-(N-Pyrrolidinesulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[(1-pyrrolidinyl)ethyl]]acetamide

15 Yield 67% (HCl salt); mp 240-242°C; ^1H NMR (CDCl_3 , 300 MHz) δ 1.70 (m, 4H), 2.00-2.45 (m, 4H), 2.94 (s, 3H), 3.25 (m, 5H), 3.90 (s, 3H), 3.99 (m, 6H), 4.15 (m, 2H), 4.30 (d, J = 10.5 Hz, 1H), 4.50 (d, J = 10.6 Hz, 1H), 6.38 (m, 1H), 7.25 (m, 3H), 7.34 (m, 3H), 7.48 (s, 1H).

Example 1352-[2-(N-Pyrrolidinesulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrrolidinyl)ethyl]]acetamide

20 Prepared from diamine (iv-b) in 49% yield ($\text{CH}_3\text{SO}_3\text{H}$ salt); mp >120°C (d); MS 532 ($\text{M}+\text{H}$) $^+$.

Example 1362-[2-(N-Dimethylsulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[(1-pyrrolidinyl)ethyl]]acetamide

25 Yield, 55% (HCl salt); mp 246-248°C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.00-2.40 (m, 4H), 2.69 (s, 3H), 2.94 (m, 4H), 3.25 (m, 1H), 3.90 (s, 3H), 4.00 (m, 6H), 4.34 (d, J = 11.0 Hz, 1H), 4.41 (d, J = 10.7 Hz, 1H), 6.35 (m, 1H), 7.20-7.40 (m, 6H), 7.45 (s, 1H).

Example 137

2-[2-(N-Dimethylsulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]]acetamide

5 Prepared from diamine (iv-b) in 45% yield (HCl salt); mp 221-223°C; MS 474 (M+H)⁺.

Example 138

2-[2-[N-(4-Methylpiperazine)]sulfamoyl]-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(pyrrolidinyl)ethyl]]acetamide

10 Yield, 62% (di HCl salt); mp 255-257°C (d); ¹H NMR (CDCl₃, 300 MHz) δ 2.00-2.38 (m, 4H), 2.77 (s, 3H), 2.95 (s, 3H), 3.05-3.28 (m, 4H), 3.30-3.48 (m, 2H), 3.55-3.80 (m, 4H), 3.95-4.15 (m, 10H), 4.20 (d, J = 10.5 Hz, 1H), 4.30 (d, J = 10.5 Hz, 1H), 6.40 (m, 1H), 7.27 (m, 2H), 7.35 (m, 2H), 7.46 (m, 3H).

15

Example 139

2-[2-[N-(4-Methylpiperazine)]sulfamoyl]-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]]acetamide

20 Prepared from diamine (iv-b) in 74% yield (di HCl salt); mp 168-171°C; MS 561 (M+H)⁺.

Example 140

2-[2-N-(Morpholinesulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(pyrrolidinyl)ethyl]]acetamide

25 Yield 75% (HCl salt), mp 229-231°C; ¹H NMR (CDCl₃, 300 MHz) δ 2.05-2.40 (m, 4H), 2.94 (m, 6H), 3.08 (m, 4H), 3.25 (m, 1H), 3.68 (m, 4H), 3.90 (s, 3H), 3.97 (s, 3H), 4.15 (m, 2H), 4.37 (m, 2H), 6.38 (m, 1H), 7.25-7.39 (m, 6H), 7.52 (s, 1H).

30

Example 141

2-[2-N-(Morpholinesulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]]acetamide

35 Prepared from diamine (iv-b) in 77% yield (HCl salt); mp 158-161°C; MS 548 (M+H)⁺.

Example 142N-Methyl-[[2-(N-sulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(pyrrolidinyl)ethyl]]acetamido]glycine

5 The desired sulfamoyl phenyl acetic acid was prepared from sulfonyl chloride (xi) ($R^1 = R^2 = OCH_3$) and sarcosine t-butyl ester followed by the hydrolysis of the methyl ester. The acid was condensed with diamine (iv-a) and the cleavage of t-butyl ester gave (21) in 80% overall yield (HCl salt); mp 231-233°C (d); MS (FAB) 534 (MH^+); 1H NMR (d_6 DMSO, 300 MHz) δ 2.05 (m, 4H), 2.77 (s, 3H), 2.81 (s, 3H), 3.50-4.35 (m, 17H), 6.15 (m, 1H), 7.25-7.55 (m, 7H).

10

Example 1432-[2-(N-Pyrrolidinesulfamoyl)-3,4,5-trimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(pyrrolidinyl)ethyl]]acetamide

15 Yield, 62% (HCl salt); mp 225-227°C; 1H NMR ($CDCl_3$, 300 MHz) δ 1.80 (m, 4H), 2.50-2.80 (m, 8H), 2.75 (s, 7H), 3.90 (s, 6H), 4.00 (s, 3H), 4.20 (m, 2H), 6.50 (m, 1H), 7.20-7.44 (m, 6H).

20

Example 1442-[2-(N-t-Butylsulfamoyl)-3,4,5-trimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(pyrrolidinyl)ethyl]]acetamide

25 Yield, 74% (HCl salt); mp 248-250°C; 1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 9H), 2.05-2.30 (m, 4H), 2.69 (s, 6H), 2.90 (m, 6H), 4.05 (m, 2H), 4.30 (d, $J = 9.5$ Hz, 1H), 4.40 (d, $J = 9.6$ Hz, 1H), 6.30 (m, 1H), 7.27 (m, 4H), 7.60 (m, 3H), 7.83 (s, 1H).

30

Example 1452-[2-(N-Methylsulfamoyl)-4-methoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(pyrrolidinyl)ethyl]]acetamide

35 Yield, 25% (CH_3SO_3H salt); mp 232-234°C; 1H NMR (d_6 DMSO, 300 MHz) δ 1.80-2.01 (m, 4H), 2.37 (s, 3H), 2.39 (s, 3H), 2.75 (s, 3H), 3.18 (m, 2H), 3.50-3.57 (m, 3H), 3.85 (m, 2H), 3.88 (s, 3H), 6.15 (m, 1H), 6.99 (m, 1H), 7.20 (m, 2H), 7.35 (m, 2H), 7.48 (m 1H), 7.68 (m, 1H).

35

Example 146**2-[4-N-(Methylsulfamoyl)-phenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-(3S)-(3-hydroxypyrrolidinyl)ethyl]acetamide**

5 The sulfamoyl acid was prepared from methyl phenyl acetate as described above and
condensed with diamine (iv-b) to give the title compound in 42% yield ($\text{CH}_3\text{SO}_3\text{H}$ salt); mp 201-
203°C; ^1H NMR ($d_6\text{DMSO}$, 300 MHz) δ 1.70-2.35 (m, 2H), 2.32 (s, 3H), 2.40 (d, J = 5.0 Hz,
3H), 2.74 (s, 3H), 3.15-3.80 (m, 5H), 3.81-4.20 (m, 3H), 4.35-4.55 (m, 1H), 5.44 and 5.55 (m,
1H), 6.13 (m, 1H), 7.50-7.45 (m, 5H), 7.47 (d, J = 8.1 Hz, 2H), 7.71 (d, J = 8.2 Hz, 1H), 9.55 (bs,
10 1H), 9.87 (bs, 1H).

Example 147**2-[2-(N-Methylsulfamoyl)-phenyl]-N-methyl-N-[(1-(2-fluorophenyl-2-[1-pyrrolidinyl)ethyl]acetamide**

15 Prepared from diamine (iv-a) (R = 2-F) in 63% yield ($\text{CH}_3\text{SO}_3\text{H}$ salt); mp 232-234°C; ^1H
NMR ($d_6\text{DMSO}$, 300 MHz) δ 1.80-2.50 (m, 4H), 2.33 (s, 3H), 2.41 (d, J = 4.9 Hz), 2.76 (s, 3H),
3.22 (m, 2H), 3.50-3.80 (m, 3H), 3.88 (s, 2H), 4.23 (m, 2H), 6.28 (m, 2H), 7.20-7.35 (m 2H),
7.35-7.50 (4H), 7.71 (d, J = 8.2 Hz, 2H), 9.33 (bs, 1H).

20

25 **Example 148**
2-[2-(N-Benzyl-N-methylsulfamoyl)-4,5-dimethoxyphenyl]-N-methyl-N-[(1S)-1-phenyl-2-[1-pyrrolidinyl)ethyl]acetamide

Yield, 46% (HCl salt); mp 188-189°C; ^1H NMR (CDCl_3 , 300 MHz) δ 2.15 (m, 4H), 2.56
(s, 3H), 2.92 (s, 3H), 3.25 (m, 1H), 3.90 (s, 3H), 4.04 (m, 10H), 4.50 (m, 2H), 6.38 (m, 1H), 7.26
(m, 11H), 7.50 (s, 1H).

30 In a composition aspect, the kappa agonist compounds of the present invention are
formulated into parenteral, local and topical formulations.

35 The compositions are formulated as injectables, as oral and rectal formulations for
systemic administration, and for local and topical administration as creams, aqueous or non-
aqueous suspension, lotions, emulsions, suspensions or emulsions containing micronized
particles, gels, foams aerosols, solids and other suitable vehicles for application to the skin, eyes,
lips and mucosa, as suppositories or cream for vaginal administration, and as combinations with
bandages, patches, bioadhesives and dressings. The compounds may be formulated in
combination with other agents, such as local anesthetics and other therapeutic agents. The other

agents may be mixed in the compositions are provided and administered prior to, simultaneously with or subsequent to administration of the compositions provided for the methods herein. Such agents include, but are not limited to: antibiotics, including cephalosporins, β -lactams, tetracyclines, vancomycins, sulfas and aminoglycosides; antivirals, including acylovir; and 5 antifungals including clotrimazole.

In a method aspect the present invention provides method to treat hyperalgesia by applying an amount of a compound or composition to a mammal to ameliorate or eliminate pain. Thus, the method of the present invention comprises a method of treating pain internally or externally present in the mammalian body including: internal injuries, such as caused by accident 10 or surgical procedures; abnormal functioning of body organs; irritation associated with inflammation following local infection, blisters, boils, or acute skin injuries, such as abrasions, burns, superficial cuts, surgical incisions, toothaches, contusions, irritations, inflammatory skin conditions, including but not limited to poison ivy, and allergic rashes and dermatitis and any condition that yields a hyperalgesic pain state and other such conditions.

15

Assessment of Anti-Hyperalgesic Activity

The pharmacological activity of the compounds of the present invention may be assessed by several art-recognized *in vitro* and *in vivo* models. Some of the typical models are described herein.

20

(a) ***In vitro* binding assay (Primary Screen)¹⁴**

The initial test of these compounds is [³H]diprenorphine binding to the cloned human kappa receptor. The compounds that inhibit binding by at least 80% at 1 μ M are titrated and K_i values are determined by Cheng-Prusoff transformations of IC_{50} values. The IC_{50} value is the 25 concentration of inhibitor that inhibits binding of radiolabel by 50% and the K_i value is the affinity of the inhibitor for the receptor. Compounds are also tested against [³H]U69593 (agonist) binding to this receptor. No compound is known to inhibit only agonist binding or antagonist binding. However, such a compound may have a unique pharmacological profile as a result of its specificity for one region of the receptor.

30 Initial specificity is determined by testing compounds using [³H]diprenorphine binding to cloned human mu and delta receptors at 10 μ M and titrating those compounds that inhibit binding

by at least 80%. Compounds that do not have K_i values at least 100-fold higher against mu and delta receptors may be more likely to have additional side effects and are not pursued to enable further evaluation of specific compounds.

5 Ref.

(14) Raynor et al., Mol. Pharmacol. 45, 330-334 (1994)

(b) **In vivo evaluation of formalin-induced nociception**

10 Administration of formalin into the paw results in a localized inflammation and a pain response that is moderate in intensity and continuous in duration. Unlike many other assays of nociception, the formalin assay measures tonic pain that is a result of tissue injury, and therefore is a model which is more relevant to clinical pain states in humans [see Tjolsen *et al.* (1992) Pain 51: 5-17]. In the rat the response to formalin-induced pain consists of spontaneous flinching 15 behavior, characterized by paw lifting and paw shaking, and a rapid vibration of the paw after drawing it under the body. The flinching response can be reliably quantitated and exhibits two peaks of activity which are indicative of acute and tonic pain [Wheeler-Aceto and Cowan (1991) Psychopharmacology 104: 35-44]. The early or acute phase lasts from 0-5 min post-formalin and is followed by a quiescent period lasting approximately 15 min. The tonic phase occurs from 20-20 35 min following formalin injection and is the interval where the number of flinching responses is maximal. This model has been characterized in several species [Tjolsen *et al.* (1992) Pain 51: 5-17] and is sensitive to the analgesic effects of opiates administered by a variety of routes, including local administration directly into the paw. In addition, the test is particularly sensitive to the effects of κ agonists [Wheeler-Aceto and Cowan (1991) Psychopharmacology 104: 35-44].

25 Inflammation is induced by subcutaneous injection of 50 μ L of a 5% formalin solution into the dorsal surface of the right hind paw of male Sprague-Dawley rats weighing 70-90 g. Injections of drug are given into the dorsal surface of the paw prior to formalin injection, and flinching behavior is quantitated by counting the number of responses that occur during the tonic phase of pain, lasting from 20-35 min after formalin injection. Results are expressed as the mean 30 percent antagonism of formalin-induced flinching calculated for individual drug-treated, formalin-injected rats using the following formula:

$$(\text{mean formalin response} - \text{mean saline response}) - \text{individual response}$$

x 100

mean formalin response - mean saline response

The mean formalin response is the mean behavioral score of vehicle-treated and formalin-injected rats. The mean saline response is the pooled behavioral score from rats injected with 50 μ L of saline into the paw.

(d) Randall-Selitto Test

Numerous variations and exemplifications of this assay are known to those of skill in this art [see, Randall *et al.* (1957) Arch. Int. Pharmacodyn. **111**: 409-419; see, also, e.g., U.S. Patent 10 No. 5,434,292, U.S. Patent No. 5,369,131, U.S. Patent No. 5,345,943, U.S. Patent No. 5,242,944 and U.S. Patent No. 5,109,135.

The pain threshold is measured in this method as the amount of pressure in g required to induce a flight reaction (struggle) when applied to the foot of an experimental animal exhibiting hyperalgesia, typically an inflamed paw, compared to a control, such as the same or equivalent 15 animal in the absence of the inflammation, and/or in the absence of a test compound.

Incremental pressure is applied to the paw with a wedge-shaped blunt piston onto the dorsal surface of the hind paw by means of a paw pressure analgesia meter. The pressure required to elicit paw withdrawal, the paw pressure threshold (PPT), is determined.

Stein and coworkers [Stein *et al.* (1988) Pharmacol. Biochem. Behav. **31**: 445-451; Stein 20 *et al.* (1989) J. Pharmacol. Exp. Ther. **248**: 1269-1275] have developed a model of peripheral inflammation and hyperalgesia in rats, which supports the role of opiates in mediating peripheral analgesia. In this protocol, modified Freund's adjuvant is used as the inflammatory stimulus, and the paw pressure test is used to assess the response of the rat to a painful pressure stimulus. The model is sensitive to opiate agonists of the μ , δ and κ subtypes, which produce analgesia upon 25 administration [Antonijevic *et al.* (1995) J. Neurosci. **15**: 165-172; Stein *et al.* (1988) Neurosci. Lett. **84**: 225-228; Stein *et al.* (1989) J. Pharmacol. Exp. Ther. **248**: 1269-1275]. Histological verification of opiate receptor localization and density have confirmed that peripheral opiate receptors are accessible on primary afferent nerve fibers and are upregulated following inflammation [Hassan *et al.* (1993) Neuroscience **55**: 185-193; Przewlocki *et al.* (1992) Neuroscience **48**: 491-500].

Experiments are conducted in rats weighing 150-250 g at the time of inoculation.

Modified Freund's complete adjuvant (FCA) is used as the inflammatory stimulus. Rats are

administered an i.pl. injection of the FCA suspension into the right hind foot. Hyperalgesia and antinociception are evaluated using the paw pressure test. The rat is gently restrained and incremental pressure is applied to the paw with a wedge-shaped blunt piston onto the dorsal surface of the hind paw by means of a paw pressure analgesia meter. The pressure required to elicit paw withdrawal, the paw pressure threshold (PPT), is determined. A cutoff pressure of 250 g is used to avoid undue stress and pain to the animal. Baseline responding is established by determining the average of three consecutive trials separated by 10 sec. The same procedure is conducted on the contralateral side and the sequence of sides is alternated between animals to control for order effects. Typically injections are not made in the contralateral (noninflamed) paw; however, in selected cases drugs may be administered to the contralateral paw to evaluate the potential for drug effects in the absence of inflammation.

Analgesic activity is determined by expressing the increase in PPT resulting from the effect of the drug as a percentage of basal preinjection thresholds.

Hyperalgesia can also be produced by inflammatory stimuli such as yeast or carrageenan, endogenous inflammatory mediators such as bradykinin or prostaglandins, or other types of chemical irritants [see Hargreaves and Joris (1993) APS Journal 2: 51-59].

(e) Acetic acid-induced writhing

This test identifies novel agents which exhibit peripheral analgesic activity against visceral or chemical pain [see Barber and Gottschlich (1986) Med. Res. Rev. 12: 525-562; Ramabadran and Bansinath (1986) Pharm. Res. 3: 263-270]. Injection of acetic acid into the peritoneal cavity is used as the noxious stimulus, and the number of writhing responses that occur in response to acetic acid are counted in order to quantify the response to pain. Compounds which possess analgesic activity reduce the number of writhing responses that occur. Opiate agonists of the μ and κ subtype exhibit analgesic activity in this model [Barber and Gottschlich (1986) Med. Res. Rev. 12: 525-562; Millan (1990) Trends Pharmacol. Sci. 11: 70-76]. Novel compounds which demonstrate potency and efficacy in this assay are potential drugs for the treatment of various pathological conditions involving peripheral pain.

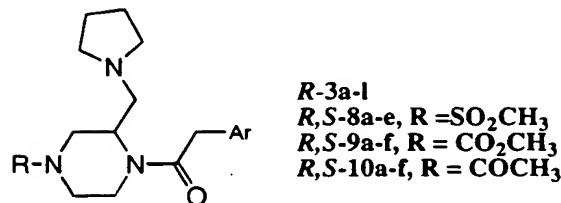
The writhing assay is adapted from the procedure originally described by Taber *et al.* [(1969) J. Pharmacol. Exp. Ther. 169: 29-38], using male CF-1 mice weighing 20-25 g. Animals are treated with various doses of drugs prior to the administration of an i.p. injection of 0.6%

acetic acid solution. Mice are then placed into observation chambers and the number of writhing responses, as defined by a full hindlimb extension and retraction, are recorded.

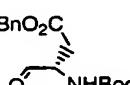
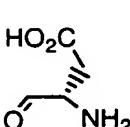
The mean number of writhing responses is calculated for vehicle-treated control mice, and the percent inhibition (% I) of writhing is calculated for each mouse that is treated with drug 5 using the following formula:

$$\% I = \frac{\text{mean control writhing responses} - \text{individual test responses}}{\text{mean control writhing responses}} \times 100$$

TABLE I
Compounds of Formula I

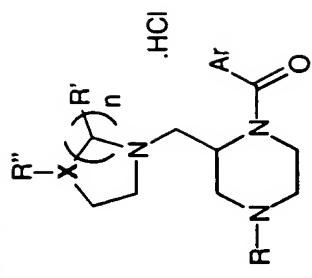


5

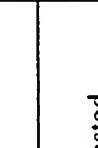
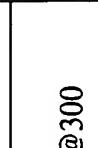
Compounds	<i>R</i>	Ar	K _i , nM ³ H-Diprenorphin	³ H-U-69,593	Late Phase Formalin A ₅₀ (mg);i.paw
GR 89696 (<i>R</i>)	CO_2CH_3	3,4 - Cl ₂	0.095, 0.10	1.6, 1.5	0.35(0.20-0.62)
(<i>R</i> -1)	Bn	3,4 - Cl ₂	57, 38	9.3	53% @ 300
(<i>R</i> -2)	H	3,4 - Cl ₂	14, 17	1.5, 1.3	57% @ 300
(<i>R</i> -3a)	SO_2CH_3	3,4 - Cl ₂	0.2, 1.3	0.19, 0.5	14 (5.6-29)
(<i>R</i> -3b)	$\text{CH}_2\text{CO}_2\text{t-Bu}$	3,4 - Cl ₂	30% @ 1uM	75% @ 1uM	75% I @ 1 μM
(<i>R</i> -3c)	$\text{CH}_2\text{CO}_2\text{H}$	3,4 - Cl ₂	62% @ 1uM	23, 21	26% @ 300
(<i>R</i> -3d)		3,4 - Cl ₂	36% @ 1uM	379, 249	Not tested.
(<i>R</i> -3e)		3,4 - Cl ₂	39% @ 1uM	37, 28	22% A @ 300
(<i>R</i> -3f)	COCH ₃	3,4 - Cl ₂	4.2, 1.4	0.11, 0.14	95% @ 300
(<i>R</i> -3g)	$\text{PO}(\text{OEt})_2$	3,4 - Cl ₂	99, 33	1.3, 1.4	54% @ 300
(<i>R</i> -3h)	COCF ₃	3,4 - Cl ₂	6.9, 1.8	0.26, 0.16	94% @ 300
(<i>R</i> -3i)	CONH ₂	3,4 - Cl ₂	56, 29	2.9	68% @ 300
(<i>R</i> -3j)	CHO	3,4 - Cl ₂	96% @ 1uM	0.40	65% @ 300

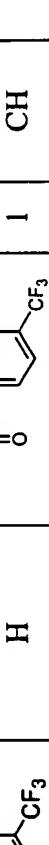
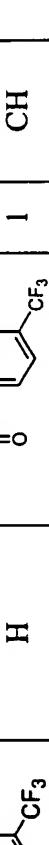
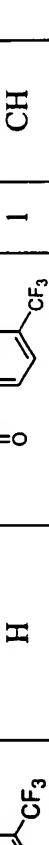
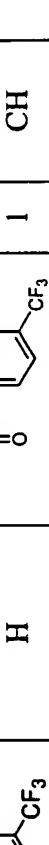
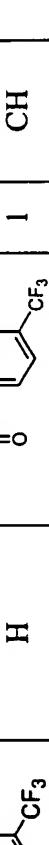
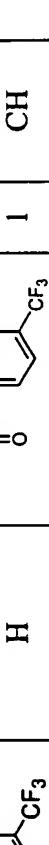
Compounds	R	Ar	Ki, nM ³ H-Diprenorphin ³ H-U-69,593		Late Phase Formalin A ₅₀ (mg);i.paw
(R-3l)	SO ₂ -Tol	3,4 - Cl ₂	120	6.2	24 % @ 300
(R,S-8a)	SO ₂ CH ₃	3,4 - Cl ₂	5.4, 4.0	0.37, 0.65	96 % @ 300
(R,S-8b)	SO ₂ CH ₃	p-SO ₂ CH ₃	41 % @ 1uM	20, 31	Not tested
(R,S-8c)	SO ₂ CH ₃	o-NO ₂	15 % @ 1uM	51 % @ 1uM	Not tested
(R,S-8d)	SO ₂ CH ₃	p-CF ₃	16, 17	1.3, 1.9	97 % @ 300
(R,S-8e)	SO ₂ CH ₃	3-indole	74 %	5.3, 3.2	Not tested
(R,S-9a)	CO ₂ CH ₃	p-SO ₂ CH ₃	11	0.37, 0.42	46 % @ 300
(R,S-9b)	CO ₂ CH ₃	p-CF ₃	0.49	0.076, 0.13	98 % @ 300
(R,S-9c)	CO ₂ CH ₃	3-indole	3.0	0.27, 0.40	95 % @ 300
(R,S-9d)	CO ₂ CH ₃	o-NO ₂	37	0.74, 0.73	93 % @ 300
(R,S-9e)	CO ₂ CH ₃	o-OCH ₃	7.3	0.46, 1.3	98 % @ 300
(R,S-9f)	CO ₂ CH ₃	o-NH ₂	4.6, 3.2	0.67, 0.41	97 % @ 300
(R,S-10a)	COCH ₃	p-SO ₂ CH ₃	27 %	2.3	6 % @ 300
(R,S-10b)	COCH ₃	p-CF ₃	26, 24	2.y0	89 % @ 300
(R,S-10c)	COCH ₃	o-CF ₃	45 % @ 1uM	16	Not tested
(R,S-10d)	COCH ₃	m-NO ₂	94 % @ 1uM	0.72	Not tested
(R,S-10e)	COCH ₃	o-NO ₂	541	24	Not tested
(R,S-10f)	COCH ₃	p-NO ₂	59 % @ 1uM	2.4	Not tested
(R,S-11)	Bn	p-CF ₃	2.2, 2.4	0.39, 0.57	92 % @ 300

TABLE IA
Compounds of Formula IA



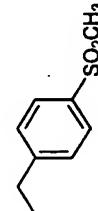
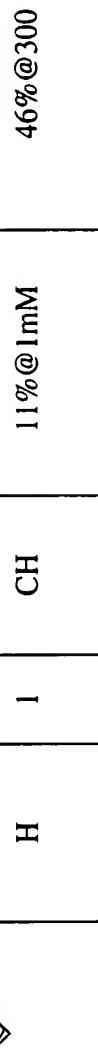
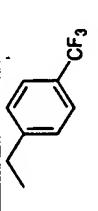
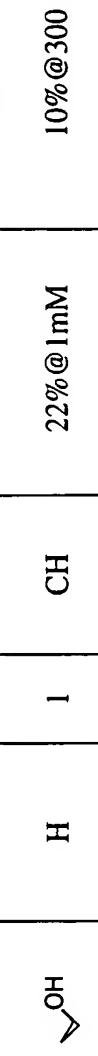
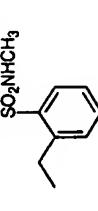
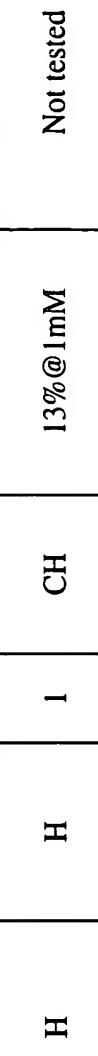
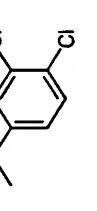
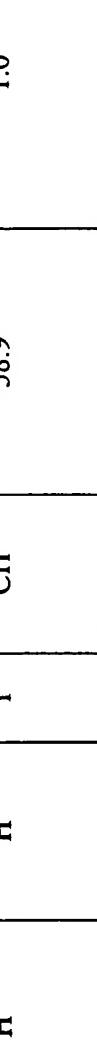
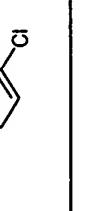
R	Ar	R'	R''	n	X	K _i (nM) (³ H)-Diprenorphin	Formalin (%A@300mM) i. paw or A ₅₀ mg/kg s.c.
CO ₂ CH ₃		H	H	1	CH ₂	248	Not tested
CO ₂ CH ₃		H	H	1	CH ₂	7	Not tested
CO ₂ CH ₃		H	H	1	CH ₂	65%@1mM	69%@300

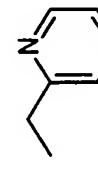
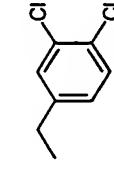
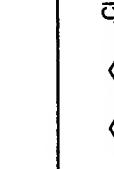
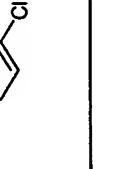
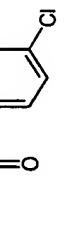
1d	CO ₂ CH ₃		H	H	1	CH ₂	7.6	77%@300
1e	CO ₂ CH ₃		H	H	1	CH ₂	14	55%@300
1f	CO ₂ CH ₃		H	H	1	CH ₂	53.5	Not tested
1g	COCF ₃		H	H	1	CH ₂	5%@1mM	Not tested
1h	COCF ₃		H	H	1	CH ₂	50	100%@300
1i	CO ₂ CH ₃		H	CO ₂ CH ₃	2	N	12%@1mM	Not tested

l _j	CO ₂ CH ₃		H		1	CH	13	Not tested
l _k	CO ₂ CH ₃			H	1	CH	51.5	95%@300
l _l	CO ₂ CH ₃			H	1	CH	3.5	1.7
l _m	CO ₂ CH ₃			H	1	CH	49.5	1.7
l _n	CO ₂ CH ₃			H	1	CH	12%@1mM	Not tested
l _o	CO ₂ CH ₃			H	1	CH	133	41%@300

1p	CO ₂ CH ₃		OH	H	1	CH	11	Not tested
1q	CO ₂ CH ₃		H		1	CH	5.2	98% @ 300
1r	COCH ₃		H	H	1	CH	43% @ 1 mM	Not tested
1s	COCH ₃		H	H	1	CH	53% @ 1 mM	Not tested
1t	COCH ₃		H	H	1	CH	1% @ 1 mM	Not tested
1u	COCH ₃		H		1	CH	1780	Not tested

1v	COCH ₃		H		1	CH	4.3	70%@300
1w	COCH ₃		H		1	CH	1156	60%@300
1x	COCH ₃		H		1	CH	36%@1mM	Not tested
1y	COCH ₃		H		1	CH	45%@1mM	Not tested
1z	COCH ₃				H	1	CH	102
1aa	COCH ₃				H	1	CH	%@1mM
								Not tested

1bb	COCH ₃			H	I	CH	11%@1mM	46%@300
1cc	COCH ₃			H	I	CH	22%@1mM	10%@300
1dd	CHO			H	I	CH	13%@1mM	Not tested
1ee				H	I	CH	58.9	1.0
1ff	allyl			H	I	CH	0.58	98%@300

1gg	COCH ₃		H	H	1	CH	27%@1mM	Not tested
1hh	CHO		H	H	1	CH	0%@1mM	Not tested
1ii (S,S ₁)	CO ₂ CH ₃		OH	H	1	CH	21.5	60%@300
1jj	SO ₂ CH ₃		H	OMs	1	CH	11.5	49%@300
1kk	SO ₂ CH ₃		H		1	CH	5.1	52%@300

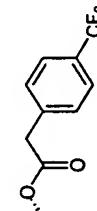
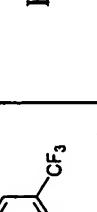
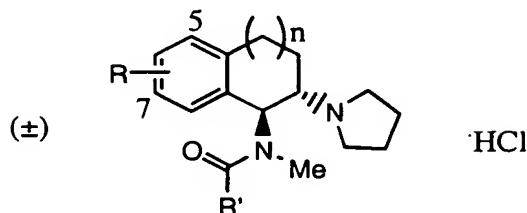
111	SO ₂ CH ₃		H	...OH	1	CH	2.86	52%@300
1m m	SO ₂ CH ₃		H		1	CH	287	Not tested
1nn	SO ₂ CH ₃		H	...OH	1	CH	2.33	7.1

TABLE II
Compounds of Formula II



Compounds	R, n	R'	K _i (nM) k [³ H]Diprenorphin	K _i (nM) k [³ H]U69,593	Late Phase Formalin A ₅₀ (mg)
II-1	7-OCH ₃ , n=1		4.7	0.8	44% A @300
II-2	7-OCH ₃ , n=1		142	20	124
II-3	7-OH, n=1		0.6	0.18	7
II-4	7-OH, n=1		549	432	Not tested
II-5	7-OCH ₂ CO ₂ H, n=1		40	7	39% @ 300
II-6	7-NO ₂ , n=1		2.8	0.8	65
II-7	7-NO ₂ , n=1		57% @ 1mM	12.8	40% A @ 300
II-8	7-NO ₂ , n=1		9.6	0.7	891
II-9	7-NH ₂ , n=1		2.2	0.35	19
II-10	7-N(CH ₂ CO ₂ Et) ₂ , n=1		4.6	0.68	37% A @ 300

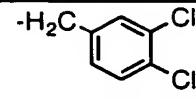
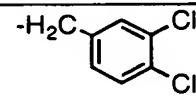
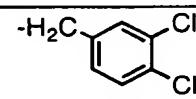
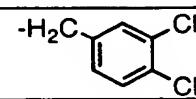
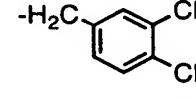
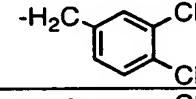
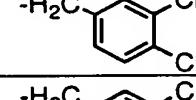
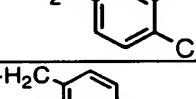
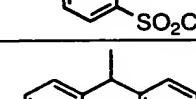
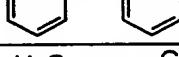
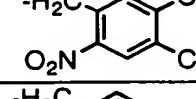
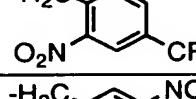
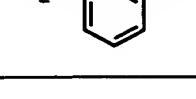
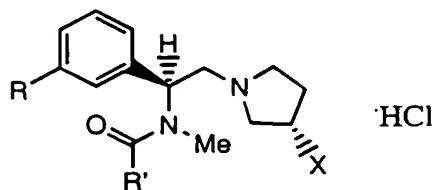
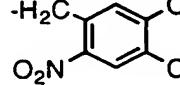
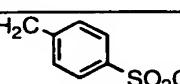
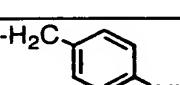
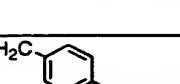
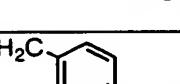
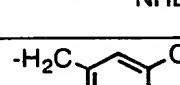
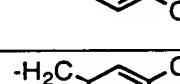
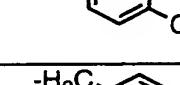
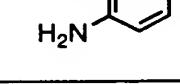
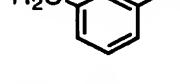
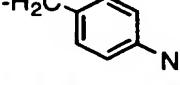
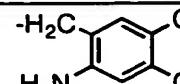
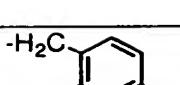
Compounds	R, n	R'	K _i (nM) k [³ H] Diprenorphin	K _i (nM) k [³ H]U69,59 3	Late Phase Formalin A ₅₀ (mg)
	n=1				
II-11	7- N(CH ₂ CO ₂ tBu) ₂ , n=1	-H ₂ C 	7.4	2.8 nM	155
II-12	7- N(CH ₂ CO ₂ H) ₂ , n=1	-H ₂ C 	3.8	0.68	232
II-13	7- NH(CH ₂) ₂ PO ₃ Et 2, n=1	-H ₂ C 	6.2	2.2	Not tested
II-14	7-NHPO ₃ Et ₂ , n=1	-H ₂ C 	2.4	0.6	34
II-15	7-SO ₂ NCH ₃ Bn, n=1 6-OMe	-H ₂ C 	48	8.0	Not tested
II-16	7-SO ₂ NCH ₃ Bn, n=1	-H ₂ C 	200	40	Not tested
II-17	-H, n=2	-H ₂ C 	8.4	2.8	21% A @ 300
II-18	R=H, n=0	-H ₂ C 	12	2.0	80% @ 300
II-19	R=H, n=0	-H ₂ C 	46% @ 1 mM	29	Not tested
II-20	R=H, n=0		29% @ 1 mM	146	Not tested
II-21	R=H, n=0	-H ₂ C 	5.7	0.74	Not tested
II-22	R=H, n=0	-H ₂ C 	75% @ 1 mM	9	Not tested
II-23 (±)- Niravoline	R=H, n=0	-H ₂ C 	13	1.8	92% @ 300

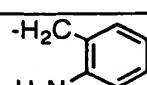
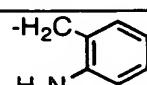
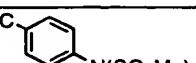
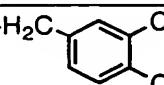
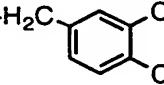
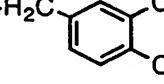
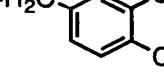
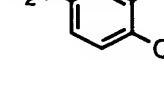
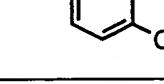
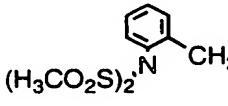
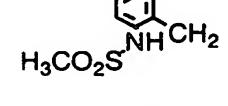
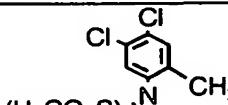
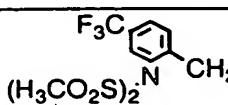
Table IIA
Compound of Formula IIA

Table III
Compounds of Formula III



Compounds	X	R	R'	K_i (nM) k [3 H]Diprenorphin	K_i (nM) k [3 H]U69.593	Late Phase Formalin A_{50} (mg)
III-1	-H	-NO ₂ (3-5% <i>p</i> -NO ₂)	-H ₂ C-	0.65	0.25	16
III-2	-H	-H	-H ₂ C-	2.9, 9.0	0.7, 1.0	29
III-3	-OH	R=H	-H ₂ C-	0.61	0.085	15
III-4	-H	-H	-H ₂ C-	0.2	0.1	5.3
III-5	-OH	R=H	-H ₂ C-	0.09	0.07	2.7 mg/ms (i-paw) 0.18 mg/kg (sc)
III-6	-H	-H	-H ₂ C-	0.20	0.26	27
III-7	-OH	R=H	-H ₂ C-	0.16	0.11	97% @ 300
III-8	-H	-H	-H ₂ C-	0.28	0.08	95% A @ 300
III-9	-H	-H	-H ₂ C-	24% @ 1 mM	1.35	Not tested
III-10	-H	-NO ₂	-H ₂ C-	35	3.2	Not tested

Compounds	X	R	R'	K _i (nM) k [³ H]Diprenorphin	K _i (nM) k [³ H]U69.593	Late Phase Formalin A ₅₀ (mg)
III-11	-H	-NO ₂		0.3	0.07	Not tested
III-12	-H	-NO ₂		31	1.5	Not tested
III-13	-H	-NO ₂		76% @ 1mM	6.4	Not tested
III-14	-H	-NO ₂		25% @ 1mM	79% @ 1mM	Not tested
III-15	-H	-NO ₂		19% @ 1 mM	168	Not tested
III-16	-H	2,3-Br ₂ 4-NH ₂		9.4	4.25	306
III-17	-H	-NH ₂		0.14	0.04	0.4
III-18	-H	-H		8.15	1.45	65
III-19	-H	-H		13	0.85	58% @ 300
III-20	-H	-H		22	1.8	52% @ 300
III-21	-H	-H		0.10	0.055	7
III-22	-H	-H		0.09	0.10	0.02 mg/Kg(s.c.)
III-23	-OH	R=H		0.18	0.12	0.02 mg/kg sc

Compounds	X	R	R'	K _i (nM) k [³ H]Diprenorphin	K _i (nM) k [³ H]U69,593	Late Phase Formalin A ₅₀ (mg)
III-24	-H	-NH ₂		20	2.6	81% @ 300
III-25 (EMD 60400)	-OH	R=H		0.8	0.175	33
III-26	-H	-NH ₂		61% @ 1 mM	43	Not tested
III-27	-H	-NH-a-D-Asp		3.65	1.05	72
III-28	-H	-NH-a-L-Asp		1.9	0.5	9.1
III-29	-H	-NH-a-L-(Asp) ₂		2.0	0.67	14
III-30	-H	-NH-b-L-Asp		2.3	0.7	47
III-31	-H	-NH-g-D-Glu				62
III-32	-H	-N(SO ₂ Me) ₂		6.45	1.2	58
III-33	-H	-H		57% @ 1 mM	6.4, 8.9	17
III-34	-H	-H		54, 40	6.8, 3.5	mg/Kg (s.c.)
III-35	-H	-H		0.38, 0.45	0.01, 0.09	28
III-36	-H	-H		0.83, 0.49	0.29, 0.43	Not tested

Compounds	X	R	R'	K _i (nM) [³ H]Diprenorphin	K _i (nM) [³ H]U69.593	Late Phase Formalin A ₅₀ (mg)
III-37	-H	-H		2.2, 3.8	0.64, 0.38	Not tested
III-38	-H	-H		63% at 1 mM	10.8	91% @ 300
III-39	-H	-H		198	32	Not tested
III-40	-H	-N(SO ₂ Me) ₂		7% @ 1 mM	58% @ 1 mM	Not tested
III-41	-H	-NHPO ₃ Et ₂		33	48	Not tested
III-42	-H	-NHPO ₃ Et ₂		56% @ 1 mM	76	Not tested
III-43 (EMD 61753)	-OH	R=H		0.52	0.34	59 mg/ms (i-paw) 28 mg/kg (sc)
III-44	-H	-H		25, 18	4.8, 3.0	67
III-45	-H	-H		55, 42, 60	7.7, 15	174
III-46	-H	-H		0.2, 0.17	0.21, 1.7	27
III-47	-OH	R=H		0.23	0.16	Not tested
III-48	-H	-H		5.4, 3.7	0.36, 0.39	39

Compounds	X	R	R'	K _i (nM) [³ H]Diprenorphin	K _i (nM) [³ H]U69.593	Late Phase Formalin A ₅₀ (mg)
III-49	-H	-H		0.43, 0.88	0.33, 0.38	29
III-50	-H	-H		0.94, 0.28	0.5, 0.07, 0.06	13
III-51	-H	-H		0.12, 0.013	0.050, 0.060	0.009 mg/Kg(s.c.)
III-52	-H	-H		0.30	0.12	97% @ 300
III-53	-H	-H		1.3	0.18	98% @ 300
III-54	-H	-H		22, 13	3.3, 1.3	90% A @ 300
III-55	-H	-H		65% @ 1mM	98% @ 1mM	43% @ 300
III-56	-H	-H		52	4.8	51% @ 300
III-57	-H	-H		5.4, 4.9	2.2, 1.2	Not tested
III-58	-H	-H		75% at 1 mM	9.0	32% @ 300
III-59	-H	-H		19	2.2	40% @ 300

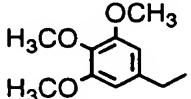
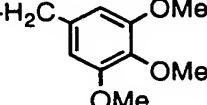
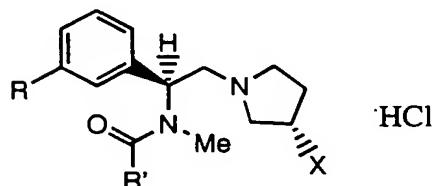
Compounds	X	R	R'	K _i (nM) k [³ H]Diprenorphin	K _i (nM) k [³ H]U69.593	Late Phase Formalin A ₅₀ (mg)
III-60	-H	-H		100% @ 1mM	91% @ 1mM	94% @ 300
III-61	-OH	R=H		1.06	0.36	Not tested

TABLE IIIA
Compounds of Formula IIIA



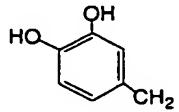
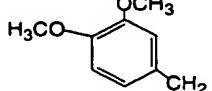
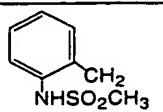
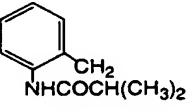
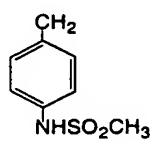
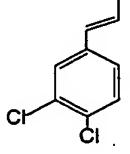
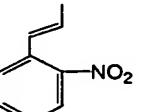
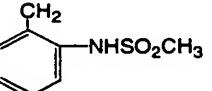
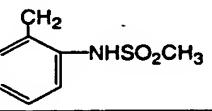
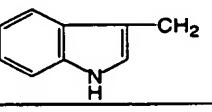
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Compound	X	R	R'	K_i (nM) [3 H]- Diprenorphin K	Late Phase Formalin A50 (mg/kg)
3a	-H	-H		1.0	1.8
3b	-H	-H		464.0	Not tested
3c	-H	-NHSO ₂ NH ₂		0.12	0.27
3d	-H	-NHSO ₂ Me		0.28	16.0
3e	-H	-NHSO ₂ Me		3.2	71% @ 300
3f	-H	-NHSO ₂ Me		0.18	8.9
3g	-H	-NHPO ₃ Et ₂		0.12	4.4
3h	-H	-NH-maleic acid		1.80	59% @ 10

3i	-H	-NH-C ₁₀ H ₁₆ O ₄ N ₂		0.14	23% @ 300
3j	-H	-NH-C ₆ H ₈ O ₃ N		2.3	38% @ 300
3k	-H	-H		18.0	Not tested
3l	-H	-H		3.8	73% @ 300
3m	-H	-H		5.1	65% @ 300
3n	-H	-NHSO ₂ CH ₃		7.3	73% @ 300
3o	-H	-H		30.5	59% @ 300
3p	-H	-H		9.7	84% @ 300
3q	-H	-H		3.2	Not tested
3r	-H	-H		7.3	10.0
3s	-H	-H			86% @ 300

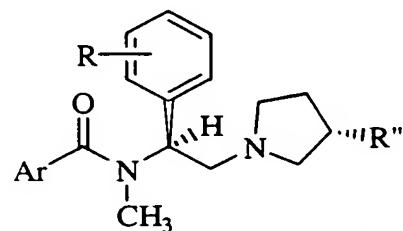
3t	-OH	-H		4.2	65% @ 300
3u	-H	-H		1.0	48% @ 300
3v	-OH	-H		46.0	36% @ 300
3w	-H	-H		2.5	90% @ 300
3y	-H	-H		0.35	Not tested
3z	-H	-H		1.7	98% @ 300
3aa	-H	-H		5279.0	Not tested
3bb	-H	-H		438.0	Not tested
3cc	-H	-H		3.1	52% @ 30

3dd	-H	-H		3.8	65% @ 300
3ee	-H	-H		26.0	34% @ 300
3ff	-OH	-H		0.17	97% @ 300
3gg	-OH	-H		5.2	1.4
3hh	-H	-H		0.56	0.11
3ii	-OH	-H		0.44	88% @ 300
3jj	-H	-H		50% @ 1 μM	Not tested
3kk	-H	-H		53% @ 1 μM	23% @ 300
3ll	-H	-H		68% @ 1 μM	77% @ 300
3mm	-H	-H		16.4	53% @ 300

3nn	-H	-H		8.8	Not tested
3oo	-H	-H		2.8	Not tested
3pp	-H	-NHSO ₂ CH ₃		4.6	Not tested
3qq	-H	-NHCOCH(CH ₃) ₂		21.0	Not tested
3π	-H	-H		0.44	2.9
3ss	-H	-H		361.5	Not tested
3tt	-H	-H		164.0	Not tested
3uu	-H	-OCH ₃		17.5	Not tested
3vv	-H	-OH		19.5	Not tested
3ww	-OH	-H		1.28	Not tested

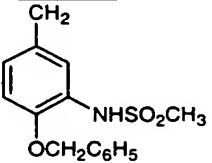
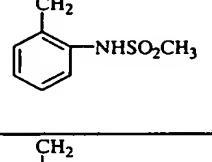
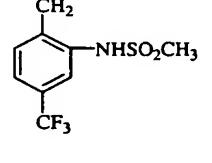
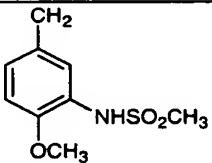
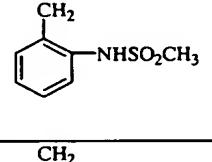
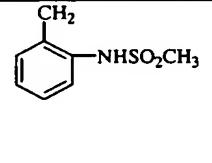
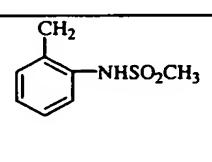
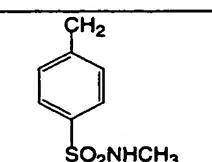
3xx	-H	-H		0.83	Not tested
3yy	-H	-H (R-isomer)		0% @ 1 μM	Not tested
3zz	-H	-OCH ₃		0.64	Not tested
3aaa	-H	-OH		0.59	Not tested
3bbb	-H	-H		4.45	Not tested
3ccc	-H	-H		1.1	Not tested
3ddd	-H	-H			Not tested

TABLE IIIIB
Compounds of Formula IIIIB and IIIB-i



Example No.	R	R''	Ar	K_i (nM) [3 H]- Diprenorphin κ	Late Phase Formalin (i. paw) A_{50} (μ g/kg)
130	H	H		1.3	46% @ 300
131	H	H		0.22	--
132	H	H		0.25	100% @ 300
133	H	OH		0.64	98% @ 300
134	H	H		0.26	99% @ 300
135	H	OH		0.66	--

136	H	H		0.44	97% @ 300
137	H	OH		0.83	--
138	H	H		1.3	80% @ 300
139	H	OH		4.2	--
140	H	H		0.56	--
141	H	OH		1.3	98% @ 300
142	H	H		13	--
143	H	H		2.1	98% @ 300
144	H	H		0.17	--
122	H	H		0.80	85% @ 300
145	H	H		20.5	83% @ 300

123	H	H		23.6	87% @ 300
124	H	H		5.6	77% @ 300
125	H	OH		5.3	81% @ 300
126	H	OH		0.61	93% @ 300
127	H	OH		0.82	94% @ 300
128 (racemic)	4-OCH ₃	H		110	56% @ 300
129A (racemic)	4-OH	H		59	46% @ 300
129B (S-isomer)	4-OH	H		75	>46% @ 300
146	H	OH		1	52% @ 300

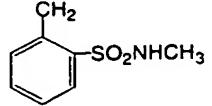
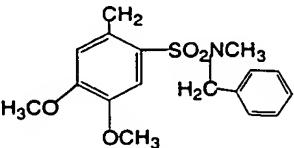
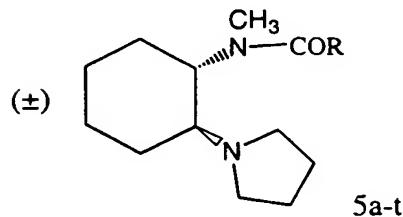
147 (racemic)	2-F	H		10	56% @ 300
148	H	H		0.83	--

TABLE IV
Compounds of Formula IV

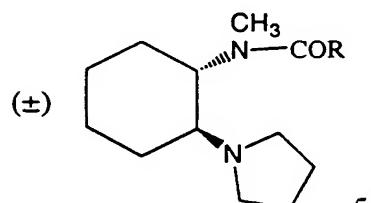


Compounds	R	K _i (nM) diprenorphine	K _i (nM) U-69593	Late Phase Formalin A ₅₀ (mg)
U-50488		4.3	0.6	Not tested
(5a)		596	100	Not tested
(5b)		1031	433	Not tested
(5c)		6.7	1.4	3.5
(5d)		10.6	1.7	72.0
(5e)		3185	675	Not tested

Compounds	R	K _i (nM) diprenorphine	K _i (nM) U-69593	Late Phase Formalin A ₅₀ (mg)
(5f)		14% @ 1μM	866	Not tested
(5g)		77% @ 1μM	3.75	59% @ 300 μg
(5h)		59% @ 1μM	13.4	58% @ 300 μg
(5i)		43% @ 1μM	5.4	73% @ 300 μg
(5j)		13% @ 1μM	48% @ 1μM	Not tested
(5k)		16% @ 1μM	216.0	Not tested
(5l)		43.5	2.35	4.7
(5m)		192.5	11.25	6.2
(5n)		61% @ 1μM	10.85	70% @ 300 μg

Compounds	R	K _i (nM) diprenorphine	K _i (nM) U-69593	Late Phase Formalin A ₅₀ (mg)
(5o)		5.65	1.4	86% @ 300 µg
(5p)		53% @ 1µM	25.0	Not tested
(5r)		50% @ 1µM	21.0	Not tested
(5s)		1171	330	Not tested
(5t)		40% @ 1mM	96	Not tested

TABLE IVA
Compounds of Formula IVA



5

Compounds	R	K _i (nM) [³ H]-Diprenorphin	Formalin (% A @ 200µg i-paw or A50 (mg/kg s.c.)
4a		77.0	26% @ 300
4b		22% @ 1µM	Not tested
4c		7% @ 1µM	NT
4d		340.5	Not tested
4f		0% @ 1µM	Not tested

4g		294.0	Not tested
4h		164.0	56% @ 300
4i		31% @ 1 μM	Not tested
4j (1S,2S)		10.30	91% @ 300
4k (1R,2R)		28% @ 1 μM	80% @ 300

FORMULATIONS OF THE PRESENT INVENTION

Effective concentrations of one or more of the compounds of the present invention or pharmaceutically acceptable derivatives thereof are mixed with a suitable pharmaceutical 5 carrier or vehicle for systemic, topical or local administration. Compounds are included in an amount effective for reducing the hyperalgesic state or other symptoms for which treatment is contemplated. The concentration of active compound in the composition will depend on absorption, inactivation, excretion rates of the active compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For topical 10 and local administration, the dosages are higher, typically at least about 5 to 10 fold, than the amount delivered when administered systemically orally.

The compounds of the present invention possess analgesic activity and can be used for the relief of pain without loss of consciousness. For example, compounds can be used to treat muscle spasm, arthritis and other musculoskeletal conditions, *e.g.*, bursitis, relieve mild to 15 moderate postoperative and postpartum pain, dysmenorrhea and pain of traumatic origin. Additionally, the compounds of the present invention can be administered for the treatment of severe pain, *e.g.*, pain associated with adenocarcinoma, amputation of a limb, and third degree burns over a major portion of the body in animals and humans.

Selected compounds of the present invention have activity as narcotic antagonists. 20 They can be used to counteract or prevent excessive central nervous system depression and respiratory depression resulting from the administration of morphine or other morphine-like drugs, *e.g.*, hydromorphone, oxymorphone, methadone and meperidine. The compounds are also capable of inducing an abstinence syndrome in narcotic addicted subjects, *i.e.*, induce withdrawal effects for diagnostic purposes.

25 The dosage of the compound of Formulas I, IA, II, IIA, III, IIIA, IIIB, IIIB-i, IV, and IVA for analgesic purposes is from about 0.001 to about 20 mg/kg body weight of the patient. The compounds of Formulas I, IA, II, IIA, III, IIIA, IIIB, IIIB-i, IV, and IVA are conveniently prepared in 5, 10, 25, 50, 75, 100 and 200 mg dosage units for administration for 1 to 4 times a day. Preferred unit dosages are from 0.05 to 10 mg/kg body weight of the patient.

30 The compounds are administered orally, parenterally, rectally and topically.

Pharmaceutical carriers or vehicles suitable for administration of the compounds and for the methods provided herein include any such carriers known to those skilled in the art to

be suitable for the particular mode of administration. In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients.

5 a) **Systemic Formulations**

The formulations of the present invention are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil-water emulsions containing suitable quantities of a compound of Formulas I, IA, II, II A, III, IIIA, 10 III B, III B-i, IV, and IV A or pharmacologically acceptable salts thereof.

Pharmaceutical dosage unit forms are prepared to provide from about 0.05 mg to about 500 mg and preferably from about 1.0 to about 200 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

Oral pharmaceutical dosage forms are either solid or liquid. The solid dosage forms 15 are tablets, capsules, granules, and bulk powders. Types of oral tablets include compressed, chewable lozenges and tablets which may be enteric-coated, sugar-coated or film-coated. Capsules may be hard or soft gelatin capsules, while granules and powders may be provided in non-effervescent or effervescent form with the combination of other ingredients known to those skilled in the art.

20 Pharmaceutically acceptable carriers utilized in tablets are binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, and wetting agents. Enteric-coated tablets, due to their enteric-coating, resist the action of stomach acid and dissolve or disintegrate in the neutral or alkaline intestines. Sugar-coated tablets are compressed tablets to which different layers of pharmaceutically acceptable substances have been applied. Film-coated tablets are compressed tablets which have been coated with a water soluble polymers. 25 Multiple compressed tablets are compressed tablets made by more than one compression cycle utilizing the pharmaceutically acceptable substances previously mentioned. Coloring agents may also be used in the above dosage forms. Flavoring and sweetening agents are used in compressed tablets, sugar-coated, multiple compressed and chewable tablets. 30 Flavoring and sweetening agents are especially useful in the formation of chewable tablets and lozenges.

Examples of binders include glucose solution, acacia mucilage, gelatin solution, sucrose and starch paste. Lubricants include talc, starch, magnesium or calcium stearate, lycopodium and stearic acid. Diluents include, for example, lactose, sucrose, starch, kaolin, salt, mannitol and dicalcium phosphate. Disintegrating agents include corn starch, potato 5 starch, bentonite, methylcellulose, agar and carboxymethylcellulose. Coloring agents include, for example, any of the approved certified water soluble FD and C dyes, mixtures thereof, and water insoluble FD and C dyes suspended on alumia hydrate. Sweetening agents include sucrose, lactose, mannitol and artificial sweetening agents such as sodium cyclamate and saccharin, and any number of spray dried flavors. Flavoring agents include natural flavors 10 extracted from plants such as fruits and synthetic blends of compounds which produce a pleasant sensation. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene laural ether. Enteric-coatings include fatty acids, fats, waxes, shellac, ammoniated shellac and cellulose acetate phthalates. Film coatings include hydroxyethylcellulose, sodium carboxymethylcellulose, 15 polyethylene glycol 4000 and cellulose acetate phthalate.

Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Aqueous solutions include, for example, elixirs and syrups. Emulsions are either oil-in water or water-in-oil.

Elixirs are clear, sweetened, hydroalcoholic preparations. Pharmaceutically acceptable carriers used in elixirs include solvents. Syrups are concentrated aqueous solutions of a sugar, for example, sucrose, and may contain a preservative. An emulsion is a two-phase system in which one liquid is dispersed in the form of small globules throughout another liquid. Pharmaceutically acceptable carriers used in emulsions are non-aqueous 20 liquids, emulsifying agents and preservatives. Suspensions use pharmaceutically acceptable suspending agents and preservatives. Pharmaceutically acceptable substances used in non-effervescent granules, to be reconstituted into a liquid oral dosage form, include diluents, sweeteners and wetting agents. Pharmaceutically acceptable substance used in effervescent 25 granules, to be reconstituted into a liquid oral dosage form, include organic acids and a source of carbon dioxide. Coloring and flavoring agents are used in all of the above dosage forms.

Solvents include glycerin, sorbitol, ethyl alcohol and syrup. Examples of preservatives include glycerin, methyl and propylparaben, benzoic acid, sodium benzoate and

alcohol. Examples of non-aqueous liquids utilized in emulsions include mineral oil and cottonseed oil. Examples of emulsifying agents include gelatin, acacia, tragacanth, bentonite, and surfactants such as polyoxyethylene sorbitan monooleate. Suspending agents include sodium carboxymethylcellulose, pectin, tragacanth, Veegum and acacia. Diluents include 5 lactose and sucrose. Sweetening agents include sucrose, syrups, glycerin and artificial sweetening agents such as sodium cyclamate and saccharin. Wetting agents include propylene glycol monostearate, sorbitan monooleate, diethylene glycol monolaurate and polyoxyethylene lauryl ether. Organic acids include citric and tartaric acid. Sources of carbon dioxide include sodium bicarbonate and sodium carbonate. Coloring agents include 10 any of the approved certified water soluble FD and C dyes, and mixtures thereof. Flavoring agents include natural flavors extracted from plants such fruits, and synthetic blends of compounds which produce a pleasant taste sensation.

Parenteral administration of the formulations of the present invention includes intravenous, subcutaneous and intramuscular administrations.

15 Preparations for parenteral administration include sterile solutions ready for injection, sterile dry soluble products ready to be combined with a solvent just prior to use, including hypodermic tablets, sterile suspensions ready for injection, sterile dry insoluble products ready to be combined with a vehicle just prior to use and sterile emulsions. The solutions may be either aqueous or nonaqueous.

20 Pharmaceutically acceptable carriers used in parenteral preparations include aqueous vehicles, nonaqueous vehicles, antimicrobial agents, isotonic agents, buffers, antioxidants, local anesthetics, suspending and dispersing agents, emulsifying agents, sequestering or chelating agents and other pharmaceutically acceptable substances.

25 Examples of aqueous vehicles include Sodium Chloride Injection, Ringers Injection, Isotonic Dextrose Injection, Sterile Water Injection, Dextrose and Lactated Ringers Injection. Nonaqueous parenteral vehicles include fixed oils of vegetable origin, cottonseed oil, corn oil, sesame oil and peanut oil. Antimicrobial agents in bacteriostatic or fungistatic concentrations must be added to parenteral preparations packaged in multiple-dose containers which include phenols or cresols, mercurials, benzyl alcohol, chlorobutanol, methyl and propyl p-
30 hydroxybenzoic acid esters, thimerosal, benzalkonium chloride and benzethonium chloride. Isotonic agents include sodium chloride and dextrose. Buffers include phosphate and citrate. Antioxidants include sodium bisulfate. Local anesthetics include procaine hydrochloride.

Suspending and dispersing agents include sodium carboxymethylcellulose, hydroxypropyl methylcellulose and polyvinylpyrrolidone. Emulsifying agents include Polysorbate 80 (Tween 80). A sequestering or chelating agent of metal ions include EDTA. Pharmaceutical carriers also include ethyl alcohol, polyethylene glycol and propylene glycol for water miscible vehicles and sodium hydroxide, hydrochloric acid, citric acid or lactic acid for pH adjustment.

The concentration of the pharmaceutically active compound is adjusted so that an injection provides an effective amount to produce the desired pharmacological effect. The exact dose depends on the age, weight and condition of the patient or animal as is known in the art.

The unit-dose parenteral preparations are packaged in an ampoule or a syringe with a needle.

All preparations for parenteral administration must be sterile, as is known and practiced in the art.

Illustratively, intravenous or intraarterial infusion of a sterile aqueous solution containing an active compound is an effective mode of administration. Another embodiment is a sterile aqueous or oily solution or suspension containing an active material injected as necessary to produce the desired pharmacological effect.

Pharmaceutical dosage forms for rectal administration are rectal suppositories, capsules and tablets for systemic effect.

Rectal suppositories are used herein mean solid bodies for insertion into the rectum which melt or soften at body temperature releasing one or more pharmacologically or therapeutically active ingredients.

Pharmaceutically acceptable substances utilized in rectal suppositories are bases or vehicles and agents to raise the melting point.

Examples of bases include cocoa butter (theobroma oil), glycerin-gelatin, carbowax, (polyoxyethylene glycol) and appropriate mixtures of mono-, di- and triglycerides of fatty acids. Combinations of the various bases may be used. Agents to raise the melting point of suppositories include spermaceti and wax. Rectal suppositories may be prepared either by the compressed method or by molding. The typical weight of a rectal suppository is about 2 to 3 gm.

Tablets and capsules for rectal administration are manufactured using the same pharmaceutically acceptable substance and by the same methods as for formulations for oral administration.

The pharmaceutically therapeutically active compounds of Formulas I, II, III and IV are administered orally, parenterally or rectally in unit-dosage forms or multiple-dosage forms. Unit-dose forms as used herein refers to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit-dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit-dose forms include ampoules and syringes individually packaged tablet or capsule. Unit-dose forms may be administered in fractions or multiples thereof. A multiple-dose form is a plurality of identical unit-dosage forms packaged in a single container to be administered in segregated unit-dose form. Examples of multiple-dose forms include vials, bottles of tablets or capsules or bottles of pint or gallons. Hence, multiple dose form is a multiple of unit-doses which are not segregated in packaging.

Compounds of the present invention in formulations may be included with other active compounds to obtain desired combinations of properties. Other active compounds with known pharmacological properties include analgesics such as aspirin, phenacetin, acetaminophen, propoxyphene, pentazocine, codeine, meperidine, oxycodone, mefenamic acid, and ibuprofen; muscle relaxants such as methocarbamol, orphenadrine, carisoprodol, meprobamate, chlorphenesin carbamate, diazepam, chlordiazepoxide and chlorzoxazone; analeptics such as caffeine, methylphenidate and pentylenetetrazol; corticosteroids such as methylprednisolone, prednisone, prednisolone and dexamethasone; antihistamines such as chlorpheniramine, cyproheptadine, promethazine and pyrilamine.

25

b) Local and Topical Formulations

Typically a therapeutically effective dosage is formulated to contain a concentration of at least about 0.1% w/w up to about 50% w/w or more, preferably more than 1% w/w of the active compound to the treated tissue. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the tissue being treated and may be determined empirically using known testing protocols or by extrapolation

from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the age of the individual treated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the formulations, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed formulations.

5 The compound may be suspended in micronized or other suitable form or may be derivatized to produce a more soluble active product or to produce a prodrug. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the hyperalgesic or other condition and may be empirically determined.

10 Compounds are typically included at concentrations 0.001% w/w or greater than 1% w/w up to 50% w/w or higher. The concentration is generally greater than the concentration for systemic administration of the compound. Preferable concentrations are in the range of 0.01% w/w to about 25% w/w, more preferably 1% w/w to 25% w/w, yet more preferably greater than about 1% w/w to about 10% w/w, and most preferably greater than 1% w/w up to about 5% w/w. Aqueous suspensions and formulations contain 1% w/w or more.

15 The resulting mixture may be a solution, suspension, emulsions or the like and are formulated as creams, gels, ointments, emulsions, solutions, elixirs, lotions, suspensions, tinctures, pastes, foams, aerosols, irrigations, sprays, suppositories, bandages, or any other formulations suitable for topical or local administration.

20 The route of administration herein is topical or local administration, and compositions are formulated in a manner suitable for each route of administration. Preferred modes of administration include topical application to the skin, eyes or mucosa, and local application to the joints, such as by intra-articular injection. Thus, typical vehicles are those suitable for pharmaceutical or cosmetic application to body surfaces or for local injection.

25 Pharmaceutical and cosmetic carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration. In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be

combined with other active ingredients. The active compound is included in the carrier in an amount sufficient to exert a therapeutically useful effect in the absence of serious toxic effects on the treated individual. The effective concentration may be determined empirically by testing the compounds using in vitro and in vivo systems, including the animal models

5 described herein.

For topical administration, the compounds may be formulated in compositions in the form of gels, creams, lotions, solids, solutions or suspensions, or aerosols. Compositions for treating human skin are formulated for topical application with an anti-hyperalgesic effective amount of one or more of the compounds selected as described herein, in an effective

10 concentration range [by weight], between about 0.1% and 80%, preferably 0.1 to 50%, more preferably greater than about 1% up to about 50% or more in a cream, ointment, lotion, gel, solution or solid base or vehicle known in the art to be non-toxic and dermatologically acceptable or suitable for application to the mucosa. Aqueous suspensions are preferably formulated at concentrations greater than about 1% w/w, more preferably 2% w/w.

15 To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the hyperalgesic condition is relieved or ameliorated. Generally, emollient or lubricating vehicles that help hydrate the skin are more preferred than volatile vehicles, such as ethanol, that dry the skin. Examples of suitable bases or vehicles for preparing compositions for use with

20 human skin are petrolatum, petrolatum plus volatile silicones, lanolin, cold cream [USP], and hydrophilic ointment [USP].

The choice of an acceptable vehicle is largely determined by the mode of application and tissue to be treated. Suitable pharmaceutically and dermatologically acceptable vehicles for topical application include those suited for use include lotions, creams, solutions, gels, tapes and the like. Generally, the vehicle is either organic in nature or an aqueous emulsion and capable of having the selected compound or compounds, which may be micronized, dispersed, suspended or dissolved therein. The vehicle may include pharmaceutically-acceptable emollients, skin penetration enhancers, coloring agents, fragrances, emulsifiers, thickening agents, and solvents.

30 For local internal administration, such as intra-articular administration, the compounds are preferably formulated as a suspension in an aqueous-based medium, such as

isotonically buffered saline or are combined with a biocompatible support or bioadhesive intended for internal administration.

Lotions

5 The lotions contain an effective concentration of one or more of the compounds. The effective concatenation is preferably effective to deliver an anti-hyperalgesic amount, typically at a concentration of between about 0.1 - 50% w/w or more of one or more of the compounds provided herein. The lotions also contain from 1% to 50% w/w, preferably from 3% to 15% w/w of an emollient and the balance water, a suitable buffer, a C₂ or C₃ alcohol, 10 or a mixture of water of the buffer and the alcohol. Any emollients known to those of skill in the art as suitable for application to human skin may be used. These include, but are not limited to, the following:

15 (a) Hydrocarbon oils and waxed, including mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, and perhydrosqualene.

15 (b) Silicone oils, including dimethylpolysiloxanes, methylphenylpolysiloxanes, water-soluble and alcohol-soluble silicone-glycol copolymers.

20 (c) Triglyceride fats and oils, including those derived from vegetable, animal and marine sources. Examples include, but are not limited to, castor oil, safflower oil, cotton seed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil and soybean oil.

25 (d) Acetoglyceride esters, such as acetylated monoglycerides.

25 (e) Ethoxylated glycerides, such as ethoxylated glyceryl monostearate.

25 (f) Alkyl esters of fatty acids having 10 to 20 carbon atoms. Methyl, isopropyl and butyl esters of fatty acids are useful herein. Examples include, but are not limited to, hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, isopropyl myristate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate.

30 (g) Alkenyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include, but are not limited to, oleyl myristate, oleyl stearate, and oleyl oleate.

(h) Fatty acids having 9 to 22 carbon atoms. Suitable examples include, but are not limited to pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidonic, behenic, and erucic acids.

(i) Fatty alcohols having 10 to 20 carbon atoms, such as but not limited to, lauryl, 5 myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-octyl dodecyl alcohols.

(j) Fatty alcohol ethers, including, but not limited to, ethoxylated fatty alcohols of 10 to 20 carbon atoms, such as, but are not limited to, the lauryl cetyl, stearyl, isostearyl, 10 oleyl, and cholesterol alcohols having attached thereto from 1 to 50 ethylene oxide groups or 1 propylene oxide groups or mixtures thereof.

(k) Ether-esters, such as fatty acid esters of ethoxylated fatty alcohols.

(l) Lanolin and derivatives, including but not limited to, lanolin, lanolin oil, 15 lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin alcohols, acetylated lanolin, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of ethoxylated alcohols-esters, hydrogenolysis of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases.

(m) Polyhydric alcohols and polyether derivatives, including, but not limited to, 20 propylene glycol, dipropylene glycol, polypropylene glycol [M.W. 2000-4000], polyoxyethylene polyoxypropylene glycols, polyoxypropylene polyoxyethylene glycols, glycerol, ethoxylated glycerol, propoxylated glycerol, sorbitol, ethoxylated sorbitol, hydroxypropyl sorbitol, polyethylene glycol [M.W. 200-6000], methoxy polyethylene glycols 350, 550, 750, 2000, 5000, poly)ethylene oxide) homopolymers [M.W. 100,000 - 5,000,000], 25 polyalkylene glycols and derivatives, hexylene glycol (2-methyl-2,4-pentanediol), 1,3-butylene glycol, 1,2,6-hexanetriol, ethohexadiol USP (2-ethyl-1,3-hexanediol), C₁₅-C₁₈ vicinal glycol and polyoxypropylene derivatives of trimethylolpropane.

(n) Polyhydric alcohol esters, including, but not limited to, ethylene glycol mono- and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol 30 [M.W. 200-6000], mono- and di-fatty esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-

fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters.

(o) Wax esters, including, but not limited to, beeswax, spermaceti, myristyl myristate, and stearyl stearate and beeswax derivatives, including, but not limited to, polyoxyethylene sorbitol beeswax, which are reaction products of beeswax with ethoxylated sorbitol of varying ethylene oxide content that form a mixture of ether-esters.

(p) Vegetable waxes, including, but not limited to, carnauba and candelilla waxes.

(q) Phospholipids, such as lecithin and derivatives.

10 (r) Sterols, including, but not limited to, cholesterol and cholesterol fatty acid esters.

(s) Amides, such as fatty acid amides, ethoxylated fatty acid amides, and solid fatty acid alkanolamides.

The lotions further preferably contain from 1% w/w to 10% w/w, more preferably from 2% w/w to 5% w/w, of an emulsifier. The emulsifiers can be nonionic, anionic or cationic. Examples of satisfactory nonionic emulsifiers include, but are not limited to, fatty alcohols having 10 to 20 carbon atoms, fatty alcohols having 10 to 20 carbon atoms condensed with 2 to 20 moles of ethylene oxide or propylene oxide, alkyl phenols with 6 to 12 carbon atoms in the alkyl chain condensed with 2 to 20 moles of ethylene oxide, mono- and di-fatty acid esters of ethylene oxides mono- and di-fatty acid esters of ethylene glycol wherein the fatty acid moiety contains from 10 to 20 carbon atoms, diethylene glycol, polyethylene glycols of molecular weight 200 to 6000, propylene glycols of molecular weight 200 to 3000, glycerol, sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan and hydrophilic wax esters. Suitable anionic emulsifiers include, but are not limited to, the fatty acid soaps, *e.g.* sodium, potassium and triethanolamine soaps, wherein the fatty acid moiety contains from 10 to 20 carbon atoms. Other suitable anionic emulsifiers include, but are not limited to, the alkali metal, ammonium or substituted ammonium alkyl sulfates, alkyl arylsulfonates, and alkyl ethoxy ether sulfonates having 10 to 30 carbon atoms in the alkyl moiety. The alkyl ethoxy ether sulfonates contain from 1 to 50 ethylene oxide units. Among 25 satisfactory cationic emulsifiers are quaternary ammonium, morpholinium and pyridinium compounds. Certain of the emollients described in preceding paragraphs also have

emulsifying properties. When a lotion is formulated containing such an emollient, an additional emulsifier is not needed, though it can be included in the composition.

The balance of the lotion is water or a C₂ or C₃ alcohol, or a mixture of water and the alcohol. The lotions are formulated by simply admixing all of the components together.

5 Preferably, the compound, is dissolved, suspended or otherwise uniformly dispersed in the mixture.

Other conventional components of such lotions may be included. One such additive is a thickening agent at a level from 1% to 10% w/w of the composition. Examples of suitable thickening agents include, but are not limited to: cross-linked carboxypolymethylene 10 polymers, ethyl cellulose, polyethylene glycols, gum, tragacanth, gum kharaya, xanthan gums and bentonite, hydroxyethyl cellulose, and hydroxypropyl cellulose.

Creams

The creams are formulated to contain concentration effective to deliver an anti-15 hyperalgesic effective amount of the compound to the treated tissue, typically at between about 0.1%, preferably at greater than 1% up to and greater than 50%, preferably between about 3% and 50%, more preferably between about 5% and 15% of one or more of the compounds provided herein. The creams also contain from 5% to 50%, preferably from 10% to 25%, of an emollient and the remainder is water or other suitable non-toxic carrier, such as 20 an isotonic buffer. The emollients, as described above for the lotions, can also be used in the cream compositions. The cream may also contain a suitable emulsifier, as described above. The emulsifier is included in the composition at a level from 3% to 50%, preferably from 5% to 20%.

25 Solutions and suspensions for topical and local administration

The solutions are formulated to contain an amount of one or more compounds effective to deliver an anti-hyperalgesic amount, typically at a concentration of between about 0.1 - 50% w/w, preferably at least more than 1% w/w, more preferably more than 2% w/w of one or more of the compounds provided herein. The balance is water, a suitable organic 30 solvent or other suitable solvent or buffer. Suitable organic materials useful as the solvent or a part of a solvent system are as follows: propylene glycol, polyethylene glycol [M.W. 200-600], polypropylene glycol [M.W. 425-2025], glycerine, sorbitol esters, 1,2,6-hexanetriol,

ethanol, isopropanol, diethyl tartrate, butanediol and mixtures thereof. Such solvent systems can also contain water.

Solutions or suspensions used for local application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, 5 polyethylene glycol, glycerine, propylene glycol or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid [EDTA]; buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Liquid preparations can be enclosed in ampoules, disposable 10 syringes or multiple dose vials made of glass, plastic or other suitable material. Suitable carriers may include physiological saline or phosphate buffered saline [PBS], and the suspensions and solutions may contain thickening and solubilizing agents, such as glucose, polyethylene glycol, and polypropylene glycol and mixtures thereof. Liposomal suspensions, may also be suitable as pharmaceutically acceptable carriers. These may be prepared 15 according to methods known to those skilled in the art.

These compositions that are formulated as solutions or suspensions may be applied to the skin, or may be formulated as an aerosol or foam and applied to the skin as a spray-on. The aerosol compositions typically contain from 25% to 80% w/w, preferably from 30% to 50% w/w, of a suitable propellant. Examples of such propellants are the chlorinated, 20 fluorinated and chlorofluorinated lower molecular weight hydrocarbons. Nitrous oxide, carbon dioxide, butane, and propane are also used as propellant gases. These propellants are used as understood in the art in a quantity and under a pressure suitable to expel the contents of the container.

Suitably prepared solutions and suspension may also be topically applied to the eyes 25 and mucosa. Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01% - 10% w/w isotonic solutions, pH about 5-7, with appropriate salts, and preferably containing one or more of the compounds herein at a concentration of about 0.1% w/w preferably greater than 1% w/w, up to 50% w/w or more. Suitable ophthalmic solutions are known [see, e.g. U.S. Patent No. 5,116,868, which describes typical compositions of 30 ophthalmic irrigation solutions and solutions for topical application]. Such solutions, which have a pH adjusted to about 7.4, contain, for example, 90-100 mM sodium chloride, 4-6 mM dibasic potassium phosphate, 4-6 mM dibasic sodium phosphate, 8-12 mM sodium citrate,

0.5-1.5 mM magnesium chloride, 1.5-2.5 mM calcium chloride, 15-25 mM sodium acetate, 10-20 mM D.L.-sodium β -hydroxybutyrate and 5-5.5 mM glucose.

The active compounds of the present invention can also be mixed with other active materials, that do not impair the desired action, or with materials that supplement the desired action, including viscoelastic materials, such as hyaluronic acid, which is sold under the trademark HEALON [solution of a high molecular weight (MW of about 3 million) fraction of sodium hyaluronate; manufactured by Pharmacia, Inc. see, e.g., U.S. Patent Nos. 5,292,362, 5,282,851, 5,273,056, 5,229,127, 4,517,295 and 4,328,803], VISCOAT [fluorine-containing (meth) acrylates, such as, 1H, 2H, 2H-heptadecafluorodecylmethacrylate; see, e.g., U.S. Patent Nos. 5,278,126, 5,273,751 and 5,214,080; commercially available from Alcon Surgical, Inc.], ORCOLON [see, e.g., U.S. Patent Nos. 5,273,056; commercially available from Optical Radiation Corporation], methylcellulose, methyl hyaluronate, polyacrylamide and polymethacrylamide [see, e.g., U.S. Patent No. 5,273,751]. The viscoelastic materials are present generally in amounts ranging from about 0.5 to 5.0% w/w, preferably 1 to 3% w/w of the conjugate material and serve to coat and protect the treated tissues. The compositions may also include a dye, such as methylene blue or other inert dye, so that the composition can be seen when injected into the eye or contacted with the surgical site during surgery.

Gels

Gel compositions can be formulated by simply admixing a suitable thickening agent to the previously described solution or suspension composition. Examples of suitable thickening agents have been previously described with respect to the lotions.

The gelled compositions contain an effective amount of one or more of an antihyperalgesic amount, typically at a concentration of between about 0.1 - 50% w/w or more of one or more of the compounds provided therein; from 5% to 75% w/w, preferably from 10% to 50% w/w, of an organic solvent as previously described; from 0.5% to 20% w/w, preferably from 1% to 10% w/w of the thickening agent; the balance being water or other aqueous carrier.

Solids

Compositions of solid forms may be formulated as stick-type compositions intended for application to the lips or other parts of the body. Such compositions contain an effective

amount of one or more of the compounds provided therein. The amount is typically an amount effective to deliver an anti-hyperperalgesic amount, typically at a concentration of between about 0.1 - 50% w/w or more of one or more of the compounds provided herein. The solids also contain from about 40% to 98% w/w, preferably from about 50% to 905 w/w, 5 of the previously described emollients. This composition can further contain from 1% to 20% w/w, preferably from 5% to 15% w/w, of a suitable thickening agent, and, if desired or needed, emulsifiers and water or buffers. Thickening agents previously described with respect to lotions are suitably employed in the composition in solid form.

Other ingredients such as preservatives, including methyl-paraben or ethyl-paraben, 10 perfumes, dyes or the like, that are known in the art to provide desirable stability, fragrance or color, or other desirable properties, such as shielding from actinic rays from the sun, to compositions for application to the skin may also be employed in a composition for such topical application.

15 Additional ingredients

Other active ingredients include, but are not limited to, antibiotics, antivirals, antifungals, anti-inflammatories, including steroidal and non-steroidal anti-inflammatories, anesthetics and mixtures thereof. Such additional ingredients include any of the following:

a. **Antibacterial agents**

20 Aminoglycosides, such as Amikacin, Apramycin, Arbekacin, Bambermycins, Butirosin, Dibekacin, Dihydrostreptomycin, Fortimicin(s), Fradiomycin, Gentamicin, Ispamicin, Kanamycin, Micronomicin, Neomycin, Neomycin Undecylenate, Netilmicin, Paromomycin, Ribostamycin, Sisomicin, Spectinomycin, Streptomycin, Streptonicozid and Tobramycin;

25 Amphenicols, such as Azidamfenicol, Chloramphenicol, Chloramphenicol Palmirate, Chloramphenicol Pantothenate, Florfenicol, Thiamphenicol;

 Ansamycins, such as Rifamide, Rifampin, Rifamycin and Rifaximin;

β -Lactams;

 Carbapenems, such as Imipenem;

30 Cephalosporins, such as 1-Carba (dethia) Cephalosporin, Cefactor, Cefadroxil, Cefamandole, Cefatrizine, Cefazedone, Cefazolin, Cefixime, Cefmenoxime, Cefodizime, Cefonicid, Cefoperazone, Ceforanide, Cefotaxime, Cefotiam, Cefpimizole, Cefpirimide,

Cefpodoxime Proxetil, Cefroxadine, Cefsulodin, Ceftazidime, Ceferam, Ceftezole, Ceftibuten, Ceftizoxime, Ceftriaxone, Cefuroxime, Cefuzonam, Cephacetrile Sodium, Cephalexin, Cephaloglycin, Cephaloridine, Cephalosporin, Cephalothin, Cephapirin Sodium, Cephadrine and Pivcefalexin;

5 Cephamycins such as Cefbuperazone, Cefmetazole, Cefminox, Cefetan and Cefoxitin; Monobactams such as Aztreonam, Carumonam and Tigemonan; Oxacephems such as Flomoxef and Moxolactam; Penicillins such as Amidinocillin, Amdinocillin, Pivoxil, Amoxicillin, Ampicillan, Apalcillin, Aspoxicillin, Azidocillan, Azlocillan, Bacampicillin, Benzylpenicillanic Acid, 10 Benzylpenicillin, Carbenicillin, Carfecillin, Carindacillin, Clometocillin, Cloxacillin, Cyclacillin, Dicloxacillin, Diphenicillin, Epicillin, Fenbenicillin, Floxicillin, Hetacillin, Lenampicillin, Metampicillin, Methicillin, Mezlocillin, Nafcillin, Oxacillin, Penamecillin, Penethamate Hydriodide, Penicillin G Benethamine, Penicillin G Benzathine, Penicillin G Benzhydrylamine, Penicillin G Calcium, Penicillin G Hydragamine, Penicillin G Potassium, 15 Penicillin G Procaine, Penicillin N, Penicillin O, Penicillin V, Penicillin V Benzathine, Penicillin V Hydrabamine, Penimepencycline, Phenethicillin, Piperacillin, Pivapicillin, Propicillin, Quinacillin, Sulbenicillin, Talampicillin, Temocillin and Ticarcillin; Lincosamides such as Clindamycin and Lincomycin; Macrolides such as Azithromycin, Carbomycin, Clarithromycin, Erythromycin(s) and 20 Derivatives, Josamycin, Leucomycins, Midecamycins, Mickamycin, Oleandomycin, Primycin, Rokitamycin, Rosaramycin, Roxithromycin, Spiramycin and Troleandomycin; Polypeptides such as Amphotericin, Bacitracin, Capreomycin, Colistin, Enduracidin, Enviomycin, Fusafungine, Gramicidin(s), Gramicidin S, Mikamycin, Polymyxin, Polymyxin β -Methanesulfonic Acid, Pristinamycin, Ristocetin, Teicoplanin, Thiomectropin, 25 Tuberactinomycin, Tyrocidine, Tyrothricin, Vancomycin, Viomycin(s), Virginiamycin and Zinc Bacitracin; Tetracyclines such as Spicycline, Chlortetracycline, Clomocycline, Demeclocycline, Doxycycline, Guamecycline, Lymecycline, Meclocycline, Methacycline, Minocycline, Oxytetracycline, Penimepencycline, Pipacycline, Rolitetracycline, Sancycline, Senociclin and 30 Tetracycline; and others such as Cycloserine, Mupirocin, Tuberin.

b. Synthetic Antibacterials

2,4-Diaminopyrimidines such as Brodimoprim, Tetroxoprim and Trimethoprim;
Nitrofurans such as Furaltadone, Furazolium, Nifuradene, Nifuratel, Nifurfoline,
Nifurpirinol, Nifurprazine, Nifurtoinol and Nitrofurantoin;

5 Quinolones and analogs thereof, such as Amifloxacin, Cinoxacin, Ciprofloxacin,
Difloxacin, Enoxacin, Fleroxacin, Flumequine, Lomefloxacin, Miloxacin, Nalidixic Acid,
Norfloxacin, Ofloxacin, Oxolinic Acid, Perfloxacin, Pipemidic Acid, Piromidic Acid,
Rosoxacin, Temafloxacin and Tosufloxacin;

Sulfonamides such as Acetyl Sulfamethoxypyrazine, Acetyl Sulfisoxazole,
10 Azosulfamide, Benzylsulfamide, Chloramine- β , Chloramine-T, Dichloramine-T,
Formosulfathiazole, N²-Formyl-sulfisomidine, N⁴- β -D-Glucosylsulfanilamide, Mafenide, 4'-
(Methyl-sulfamoyl)sulfanilanilide, p-Nitrosulfathiazole, Noprylsulfamide,
Phthalylsulfacetamide, Phthalylsulfathiazole, Salazosulfadimidine, Succinylsulfathiazole,
Sulfabenzamide, Sulfacetamide, Sulfachlorpyridazine, Sulfachrysoidine, Sulfacytine,
15 Sulfadiazine, Sulfadicramide, Sulfadimethoxine, Sulfadoxine, Sulfaethidole, Sulfaguanidine,
Sulfaguanol, Sulfalene, Sulfaloxic Acid, Sulfamerazine, Sulfameter, Sulfamethazine,
Sulfamethizole, Sulfamethomidine, Sulfamethoxazole, Sulfamethoxypyridazine,
Sulfametrole, sulfamidochrysoidine, Sulfamoxole, Sulfanilamide,
Sulfanilamidomethanesulfonic Acid Triethanolamine Salt, 4-Sulfanilamidosalicylic Acid,
20 N⁴-Sulfanilylsulfanilamide, Sulfanilylurea, N-Sulfanilyl-3,4-xylamide, Sulfanitran,
Sulfaperine, Sulfaphenazole, Sulfaproxyline, Sulfapyrazine, Sulfapyridine, Sulfasomizole,
Sulfasymazine, Sulfathiazole, Sulfathiourea, Sulfatolamide, Sulfisomidine and Sulfisoxazole;
Sulfones, such as Acedapsone, Acediasulfone, Acetosulfone, Dapsone,
Diatyphosulfone, Glucosulfone, Solasulfone, Succisulfone, Sulfanilic Acid, p-
25 Sulfanilylbenzylamine, p,p'-sulfonyldianiline-N,N'digalactoside, Sulfoxone and
Thiazolsulfone;
Others such as Clofoctol, Hexedine, Magainins, Methenamine, Methenamine
Anhydromethylene-citrate, Methenamine Hippurate, Methenamine Mandelate, Methenamine
Sulfosalicylate, Nitroxoline, Squalamine and Xibornol.

c. Antifungal (antibiotics)

Polyenes such as Amphotericin-B, Candicidin, Dermostatin, Filipin, Fungichromin, Hachimycin, Hamycin, Lucensomycin, Mepartricin, Natamycin, Nystatin, Pecilocin, Perimycin; and others, such as Azaserine, Griseofulvin, Oligomycins, Pyrrolnitrin, Siccanin,

5 Tubercidin and Viridin.

d. Antifungal (synthetic)

Allylamines such as Naftifine and terbinafine;

Imidazoles such as Bifonazole, Butoconazole, Chlordantoin, Chlormidazole,

10 Cloconazole, Clotrimazole, Econazole, Enilconazole, Finticonazole, Isoconazole, Ketoconazole, Miconazole, Omoconazole, Oxiconazole Nitrate, Sulconazole and Tioconazole;

Triazoles such as Fluconazole, Itraconazole, Terconazole;

Others such as Acrisorcin, Amorolfine, Biphenamine, Bromosalicylchloranilide,

15 Buclosamide, Chlophenesin, Ciclopirox, Cloxyquin, Coparaffinate, Diamthazole, Dihydrochloride, Exalamide, Flucytosine, Halethazole, Hexetidine, Loflucarban, Nifuratel, Potassium Iodide, Propionic Acid, Pyrithione, Salicylanilide, Sultentine, Tenonitrozole, Tolciclate, Tolindate, Tolnaftate, Tricetin, Ujothion, and Undecylenic Acid.

20 **e. Antiglaucoma agents**

Antiglaucoma agents, such as Dapiprazole, Dichlorphenamide, Dipivefrin and Pilocarpine.

f. Anti-inflammatory agents

25 Corticosteroids, aminoarylcarboxylic Acid Derivatives such as Etofenamate, Meclofenamic Acid, Mefanamic Acid, Niflumic Acid;

Arylacetic Acid Derivatives such as Acemetacin, Amfenac, Cinmetacin, Clopirac, Diclofenac, Fenclofenac, Fenclorac, Fenclozic Acid, Fentiazac, Glucametacin, Isozepac, Lonazolac, Metiazinic Acid, Oxametacine, Proglumetacin, Sulindac, Tiaramide and

30 Tolmetin;

Arylbutyric Acid Derivatives such as Butibufen and Fenbufen;

Arylcarboxylic Acids such as Clidanac, Ketorolac and Tinoridine;

Arylpropionic Acid Derivatives such as Bucloxic Acid, Carprofen, Fenoprofen, Flunoxaprofen, Ibuprofen, Ibuproxam, Oxaprozin, Piketoprofen, Pirprofen, Pranoprofen, Protizinic Acid and Tiaprofenic Acid;

Pyrazoles such as Mepirizole;

5 Pyrazolones such as Clofezone, Feprazole, Mofebutazone, Oxyphenbutazone, Phenylbutazone, Phenyl Pyrazolidinones, Suxibuzone and Thiazolinobutazone;

Salicylic Acid Derivatives such as Bromosaligenin, Fendosal, Glycol Salicylate, Mesalamine, 1-Naphthyl Salicylate, Olsalazine and Sulfasalazine;

Thiazinecarboxamides such as Droxicam, Isoxicam and Piroxicam;

10 Others such as e-Acetamidocaproic Acid, S-Adenosylmethionine, 3-Amino-4-hydroxybutyric Acid, Amixetrine, Bendazac, Bucolome, Carbazones, Difenpiramide, Ditazol, Guaiazulene, Heterocyclic Aminoalkyl Esters of Mycophenolic Acid and Derivatives, Nabumetone, Nimesulide, Orgotein, Oxaceprol, Oxazole Derivatives, Paranyline, Pifoxime, 2-substituted-4, 6-di-tertiary-butyl-s-hydroxy-1,3-pyrimidines, Proquazone and Tenidap.

15

g. Antiseptics

Guanidines such as Alexidine, Ambazole, Chlorhexidine and Picloxydine;

20 Halogens/Halogen Compounds such as Bornyl Chloride, Calcium Iodate, Iodine, Iodine Monochloride, Iodine Trichloride, Iodoform, Povidone-Iodine, Sodium Hypochlorite, Sodium Iodate, Symclosene, Thymol Iodide, Triclocarban, Triclosan and Troclosene Potassium;

Nitrofurans such as Furazolidone, 2-(Methoxymethyl)-5-Nitrofuran, Nidroxyzone, Nifuroxime, Nifurzide and Nitrofurazone;

25 Phenols such as Acetomeroctol, Chloroxylenol, Hexachlorophene, 1-Naphthyl Salicylate, 2,4,6-Tribromo-m-cresol and 3',4',5--Trichlorosalicylanilide;

Quinolines such as Aminoquinuride, Chloroxine, Chlorquinadol, Cloxyquin, Ethylhydrocupreine, Halquinol, Hydrastine, 8-Hydroxyquinoline and Sulfate; and others, such as Boric Acid, Chloroazodin, m-Cresyl Acetate, Cupric sulfate and Ichthammol.

30

h. Antivirals

Purines/Pyrimidinones, such as 2-Acetyl-Pyridine 5-((2-pyridylamino)thiocarbonyl) Thiocarbonohydrazone, Acyclovir, Dideoxyadenosine, dideoxycytidine, Dideoxyinosine, Edoxudine, Floxuridine, Ganciclovir, Idoxuridine, MADU, Pyridinone, Trifluridine,

5 Vidrarbine and Zidovudline;

Others such as Acetylleucine Monoethanolamine, Acridinamine, Alkylisooxazoles, Amantadine, Amidinomycin, Cuminaldehyde Thiosemicarzone, Foscarnet Sodium, Kethoxal, Lysozyme, Methisazole, Moroxydine, Podophyllotoxin, Ribavirin, Rimantadine, Stallimycin, Statolon, Thymosins, Tromantadine and Xenozoic Acid.

10

Combinations and kits

The compounds and compositions containing the compounds may also be coated on bandages, mixed with bioadhesives or included in dressings. Thus, combinations of bandages, bioadhesives, dressings and other such materials and the compositions formulated 15 as described herein are provided. Kits containing these combinations, which may also include compositions containing the above listed agents, are also provided.

Articles of manufacture

The compounds and compositions provided herein may be packaged as articles of 20 manufacture containing packaging material, one or more of the compounds provided herein, which is effective for ameliorating peripheral hyperalgesia, within the packaging material, and a label that indicates that the compound, N-oxide, acid, salt or other derivative thereof is used for treating hyperalgesic conditions.

25

Methods of treatment

Compositions for use with human skin preferably may be applied at least once per day, or if necessary, to achieve the desired result, more often, to the areas of the skin for which treatment is sought. It is understood that the precise treatment regimen depends upon the individual treated and may be ascertained empirically depending upon the formulation, 30 and particularly, the age of the treated individual. Any regimen is acceptable as long as the desired anti-hyperalgesic effects are achieved without substantial deleterious or sustained undesirable side effects.

The methods for treating human skin are practiced by applying to the skin, preferably at least daily, a composition suitable for human skin treatment or treatment of mucosal membranes and other body surface tissues, including the vagina, rectum, mouth, eyes and other such tissues. The compositions may be injected into joints or other inflamed areas.

5 Compositions may be combined with bandages, bioadhesives and other dressings and applied to the body in combination therewith.

The following examples are included for illustrative purposes only and are not intended to limit the scope of the invention.

10 Example A - Capsules

Active Compound 2.5 gm

Corn starch 23.0 gm

Lactose 145.0 gm

Talc 15.0 gm

15 Magnesium stearate 3.0 gm

The ingredients were mixed and were encapsulated using techniques practiced in the art.

20 Example B - Tablet

Active Compound 150 gm

Lactose 125 gm

Corn starch 50 gm

Magnesium stearate 2.0 gm

25 Liquid Petrolatum 2.0 gm

The ingredients were mixed, then put through U.S. Standard Screens to produce fine granules. The granules were compressed into tablets, each tablet containing about 150 mg of an active compound of the present invention.

30

Example C - Syrup

Active Compound 25 gm

Lemon Oil 2 ml
Sucrose 650 gm
Citric Acid 4 gm
Benzoic Acid 3 gm
5 Tragacanth 16 gm
Deionized water q.s. 1000 ml

The ingredients, without the active compound, are dispersed in water to make about 800 to 900 ml of solution. The active compound is then added and the solution is stirred into 10 a syrup. Water is then added to make 1000 ml of the syrup.

Example D - Parenteral Solution

Active Compound 30 gm
Methylparaben 3 gm
15 Propylparaben 1 gm
Lidocaine 5 gm
Deionized water q.s. 1000 ml

The ingredients are dissolved in water to provide a solution followed by sterilization 20 by filtration.

Example E - Rectal Suppository

Active Compound 80 gm
Propylene glycol 95 gm
25 Polyethylene glycol 4000 1800 gm

The active compound is added to the propylene glycol and milled until a finely divided uniform mixture is formed. The polyethylene glycol 4000 is melted and the propylene glycol dispersion is added with stirring to obtain a suspension. The suspension is 30 poured into molds, allowed to solidify and removed from the molds for packaging.

Example F - Water-washable ointment

	Active Compound	1.4 % w/w
	Lanolin alcohol	0.15 w/w
	Emulsifying wax NF	7.5% w/w
	PEG-20 glycerides	5.0% w/w
5	Petrolatum	86.0% w/w

The ingredients are melted together and mixed well until the resulting ointment congeals.

10 **Example G - Oil-in-water cream**

	Active Compound	10.0% w/w
	Benzyl alcohol	4.0% w/w
	Propylene glycol	10.0% w/w
	Polyethylene glycol 400	10.0% w/w
15	Petrolatum	20.0% w/w
	Stearyl alcohol	10.0% w/w
	Poloxamer	10.0% w/w
	Water q.s.	100
	Buffer to pH	7.0% w/w

20

In preparing the oil-in-water cream, water, propylene glycol and polyethylene glycol 400 are heated to about 70 to 80°C, followed by adding a mixture of petrolatum, stearyl alcohol and poloxamer and the mixture is stirred until homogeneous. The active compound in benzyl alcohol is added and the mixture is homogenized. The pH is then adjusted with a buffer to about 7.0.

25

Example H - Aqueous gel

	Active Compound	10.0% w/w
	Benzyl alcohol	4.0% w/w
30	Hydroxyethyl cellulose	3.0% w/w
	Water q.s.	100
	Buffer to pH	7.0% w/w

The aqueous gel is prepared by mixing the active compound, benzyl alcohol and adding the mixture to buffered water. Hydroxyethyl cellulose is then added with stirring until the mixture gels.

5 The disclosures of each patent, patent application and publication cited or described in this document are hereby incorporated herein by reference, in their entirety.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims.